EXHIBIT 1

EXHIBIT 1 OF PROPOSED JOINT PRETRIAL ORDER
STATEMENT OF UNCONTESTED FACTS

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES INC., GALDERMA LABORATORIES, L.P. and SUPERNUS PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	C.A. No. 11-1106 (LPS)
v.	)	REDACTED [redacted]
AMNEAL PHARMACEUTICALS, LLC. and AMNEAL PHARMACEUTICALS CO. (I) PVT. LTD.,	)	
Defendants.	)	

STATEMENT OF UNCONTESTED FACTS

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I. PARTIES

1. Galderma Laboratories Inc. ("GLI") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 14501 North Freeway, Fort Worth, Texas 76177.

2. Galderma Laboratories, L.P. ("GLLP") is a privately held partnership registered in the state of Texas, having a principal place of business at 14501 North Freeway, Fort Worth, Texas 76177.

3. Supernus Pharmaceuticals, Inc. ("Supernus") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1550 East Gude Drive, Rockville, Maryland 20850.[1]

4. Amneal Pharmaceuticals, LLC ("Amneal Pharma") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 85 Adams Avenue, Hauppauge, NY 11788.

5. Amneal Pharmaceuticals Co. (I) PVT. Ltd. ("Amneal India") is an Indian corporation and a wholly-owned subsidiary and agent of Amneal Pharma, having a principal place of business at 882/1-871 Village Rajoda, Near Hotel Kankavati, Taluka: Bavla, District Ahmedabad-382220, Gujarat, India.[2]

II. PATENTS-IN-SUIT

6. U.S. Application Number 10/819,620 ("the '620 application"), from which U.S. Patent No. 7,749,532 ("the '532 patent") issued, was filed on April 7, 2004.

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[1] GLI, GLLP and Supernus are collectively referred to herein as "Plaintiffs."

[2] Amneal Pharma and Amneal India are collectively referred to herein as "Amneal."

7. The '532 patent claims priority to U.S. Provisional Application No. 60/460,963 ("the '963 provisional application"), filed on April 7, 2003, and U.S. Provisional Application No. 60/547,964 ("the '964 provisional application"), filed on February 26, 2004.

8. The '532 patent issued on July 6, 2010, naming Rong-Kun Chang, Arash Raoufinia, and Niraj Shah as inventors, and listing Supernus Pharmaceuticals, Inc. as assignee.

9. The '532 patent is set to expire on December 19, 2027.

10. GLI is the licensee of the '532 patent.

11. Plaintiffs have the right to sue and recover for any infringement of the '532 patent.

12. U.S. Application Number 12/155,676 ("the '676 application"), from which U.S. Patent No. 8,206,740 ("the '740 patent") issued, was filed on June 6, 2008. The '676 application is a continuation of the '620 application, filed on April 7, 2004.

13. The '740 patent claims priority to the '963 provisional application, filed on April 7, 2003, and the '964 provisional application, filed on February 26, 2004.

14. The '740 patent issued on June 26, 2012, naming Rong-Kun Chang, Arash Raoufinia, and Niraj Shah as inventors, and listing Supernus Pharmaceutical, Inc. as assignee.

15. The '740 patent is set to expire on December 24, 2025.

16. GLI is the licensee of the '740 patent.

17. Plaintiffs have the right to sue and recover for any infringement of the '740 patent.

III. CLAIM CONSTRUCTION

18. The term "steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml," as it appears in claims 1, 15, and 20 of the '532 patent, and in claims 1, 19, and 22 of the '740 patent, is construed to mean "steady state plasma concentrations

of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml," as agreed upon by the parties.

19. The term "steady state blood levels of the doxycycline of between 0.3 µg/ml to 0.8 µg/ml," as it appears in claims 4 and 18 of the '532 patent, and in claims 2 and 21 of the '740 patent, is construed to mean "steady state plasma concentrations of the doxycycline of between 0.3 µg/ml and 0.8 µg/ml," as agreed upon by the parties.

20. The Court construed the term "pellets," appearing in claims 1-3, 15, 17, and 20 of the '532 patent, and in claims 7 and 10 of the '740 patent, to mean "one or more of a small solid dosage form of reasonable size and robustness suitable for incorporation into, e.g., a capsule or tablet." (D.I. 190.)

21. The Court construed the term "pellet," appearing in claim 6 of the '740 patent, to mean "one or more of a small solid dosage form of reasonable size and robustness suitable for incorporation into, e.g., a capsule or tablet." (D.I. 190.)

22. The Court concluded that the term "coated with at least one enteric polymer," appearing in claims 1, 15, and 20 of the '532 patent, does not require construction. (D.I. 190.)

IV. ORACEA®

23. Oracea® and its FDA-approved use are a commercial embodiment of the Chang patents.

24. The active ingredient in Oracea® is doxycycline.

25. Oracea® is a capsule dosage form for oral administration.

26. Oracea® is an oral pharmaceutical composition of doxycycline.

27. Oracea® is indicated for once daily use.

28. Oracea® is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients.

29. Oracea® is a hard gelatin capsule filled with two types of doxycycline beads (30 mg immediate-release beads and 10 mg delayed-release beads).

30. Oracea® contains 10 mg doxycycline delayed-release beads that are coated with an enteric polymer.

31. Oracea® contains one or more pharmaceutical excipients.

32. Oracea® contains inactive ingredients including at least hypromellose, methacrylic acid copolymer, polyethylene glycol, Polysorbate 80, sugar spheres, talc, titanium dioxide, and triethyl citrate.

33. Oracea® contains hypromellose (i.e., hydroxypropyl methylcellulose), which functions as a binder.

34. Oracea® contains 10 mg doxycycline delayed-release beads that are coated with methacrylic acid copolymer dispersion, Type C, which functions as an enteric coating polymer.

35. Oracea® contains an amount of doxycycline that, when administered once daily, will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml.

36. Oracea® is administered in an amount that is effective to treat the papules and pustules of rosacea.

V. AMNEAL'S GENERIC PRODUCT

37. Amneal submitted Abbreviated New Drug Application ("ANDA") No. 203-278 to the U.S. Food and Drug Administration ("FDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act ("FFDCA") seeking FDA approval for the commercial manufacture, use and sale of a generic version of Oracea® ("Amneal's Generic Product") before the expiration of the '532 and '740 patents.

38. ANDA No. 203-278 describes a manufacturing process for the production of Amneal's Generic Product.

39. ANDA No. 203-278 identifies REDACTED as the manufacturer of its Generic Product.

40. If approved, Amneal's Generic Product will contain the package insert approved by the FDA for Amneal's Generic Product ("Amneal's Label").

41. The active ingredient in Amneal's Generic Product is doxycycline.

42. Amneal's Generic Product has been formulated to be administered orally

43. Amneal believes its Generic Product [redacted]

44. [redacted]

45. Amneal's Generic Product is [redacted]

46. [redacted]

47. Amneal's Generic Product consists of (i) [redacted]

48. Amneal's Generic Product comprises [redacted]

49. [redacted]

50. REDACTED

51. Amneal's Generic Product REDA

52. Amneal's Generic Product REDACTED

53. Amneal's Generic Product REDA

54. Amneal's Generic Product REDA

55. If approved by FDA, Amneal's Generic Product would be REDACTED

56. The production process of Amneal's Generic Product REDACTED

VI. ASSERTED PRIOR ART

57. Periostat® is a 20 mg immediate-release formulation of doxycycline, indicated for twice-daily administration for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

58. Periostat® was initially developed by CollaGenex Pharmaceuticals, Inc. ("CollaGenex").

59. In 2008, Plaintiff GLLP acquired New Drug Application ("NDA") No. 50-783 for Periostat® (doxycycline hyclate tablets, 20 mg) and NDA No. 50-805 for Oracea® (30 mg immediate release, 10 mg delayed release doxycycline capsules).

60. NDA No. 50-744 for Periostat® (doxycycline hyclate capsules, 20 mg) was approved by FDA on September 30, 1998.

61. Periostat® is effective at treating rosacea at a dose of 20 mg administered twice daily.

62. On April 5, 2001, CollaGenex filed U.S. Provisional Patent Application No. 60/281,854 ("the '854 application").

63. The '854 application is titled "Controlled Delivery of Tetracycline and Tetracycline Derivatives," and names Robert Ashley as an inventor.

64. On April 5, 2002, CollaGenex filed U.S. Patent Application No. PCT/US2002/10748, which published as WO 02/083106 on October 24, 2002 ("the '106 application").

65. The '106 application claims priority to the '854 application and names Robert A. Ashley as an inventor.

66. The U.S. national stage of the '106 application is U.S. Patent Application No. 10/474,240 ("the '240 application").

67. On April 5, 2002, CollaGenex filed U.S. Patent Application No. 10/117,709, which issued as U.S. Patent No. 7,232,572 ("the '572 patent").

68. The '572 patent is entitled "Methods of Treating Rosacea," and names Robert A. Ashley as an inventor.

69. The '572 patent claims priority to U.S. Provisional Application No. 60/281,916, dated April 5, 2001, and U.S Provisional Patent Application No. 60/325,489, dated September 26, 2001.

70. U.S. Patent Application No. PCT/US2002/0747 was filed on April 5, 2002, and published on October 17, 2002, as WO 02/080932 ("the '932 application").

71. The '932 application is titled "Methods of Treating Acne" and names Robert A. Ashley as an inventor.

72. U.S. Patent No. 5,348,748, issued September 20, 1994 ("the '748 patent"), and is titled "Pulsatile Once-a-Day Delivery Systems for Minocycline."

EXHIBIT 2

EXHIBIT 2 OF PROPOSED JOINT PRETRIAL ORDER
PLAINTIFFS' ISSUES OF FACT TO BE LITIGATED AT TRIAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES INC., GALDERMA LABORATORIES, L.P. and SUPERNUS PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	C.A. No. 11-1106 (LPS)
v.	)	REDACTED [redacted]
AMNEAL PHARMACEUTICALS, LLC. and AMNEAL PHARMACEUTICALS CO. (I) PVT. LTD.,	)	
Defendants.	)	

PLAINTIFFS' ISSUES OF FACT TO BE LITIGATED AT TRIAL

TABLE OF CONTENTS

I. PARTIES AND PATENTS[1]

1. U.S. Patent No. 7,749,532 ("the Chang '532 patent") claims priority to U.S. Provisional Application No. 60/460,963, filed on April 7, 2003, and U.S. Provisional Application No. 60/547,964, filed on February 26, 2004.[2]

2. A request for a Certificate of Correction for the Chang '532 patent was filed on February 1, 2011. A Certificate of Correction for the Chang '532 patent issued from the PTO on March 15, 2011.

3. Supernus Pharmaceuticals, Inc. ("Supernus") is the current assignee of the Chang '532 patent.

4. Galderma Laboratories Inc. ("GLI") is the licensee of the Chang '532 patent.

5. U.S. Patent No. 8,206,740 ("the Chang '740 patent") claims priority to U.S. Application No. 10/819,620, filed on April 7, 2004, issued as the Chang '532 patent, U.S. Provisional Application No. 60/460,963, filed on April 7, 2003, and U.S. Provisional Application No. 60/547,964, filed on February 26, 2004.

6. Supernus is the current assignee of the Chang '740 patent.

7. GLI is the licensee of the Chang '740 patent.

8. Galderma Laboratories, L.P. ("GLLP") currently holds New Drug Application ("NDA") 50-805 on Oracea® brand doxycycline capsules ("Oracea®"), which was approved by the U.S. Food and Drug Administration ("FDA") on May 26, 2006.

9. GLLP is the exclusive distributor of Oracea® in the United States.

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[1] To the extent any of the issues of law set forth in Exhibit 4 may be considered issues of fact, Plaintiffs incorporate them herein by reference. To the extent any issues of fact here may be considered issues of law, Plaintiffs incorporate them in Exhibit 4.

[2] Plaintiffs reserve the right to supplement this statement and to present evidence to contest and rebut any different or additional facts Defendants intend or attempt to introduce.

10. Abbreviated New Drug Application ("ANDA") No. 203-278 included allegations under § 505(j)(2)(A)(vii)(IV) of the FFDCA concerning the Chang '532 patent ("the Chang '532 patent Paragraph IV Certification"). Galderma received notice of ANDA No. 203-278 and the '532 patent Paragraph IV Certification by letter dated September 27, 2011 ("the Chang '532 patent Notice Letter").

11. ANDA No. 203-278 was amended to include allegations under § 505(j)(2)(A)(vii)(IV) of the FFDCA concerning the Chang '740 patent ("the Chang '740 patent Paragraph IV Certification").

12. Galderma received a supplemental notice of a Paragraph IV Certification regarding the Chang '740 patent by letter dated September 14, 2012 ("the Chang '740 patent Notice Letter").

II. ROSACEA AND ITS TREATMENT

13. Historically, rosacea has been treated by oral administration of antibiotics and/or administration of topical gels and creams to treat the signs and symptoms of the disease. *See* PTX 172 at GLD0223641-GLD0223643.

14. Topical treatments for rosacea often have side effects that may exacerbate rosacea symptoms, including redness and irritation. *See* PTX 205; PTX 206.

15. Oral doses of doxycycline indicated for the treatment of infections (*e.g.*, 50 or 100 mg doxycycline tablets) were also commonly used to treat rosacea, typically administered in amounts of 100 mg or 200 mg per day. *See* PTX 172 at GLD0223641.

16. Infections are usually of short duration and the normal recommended course of antibiotics consists of short-term administration. *See* PTX 167 at GLD0223637.

17. Rosacea is not an infection, but a chronic inflammatory disorder, and requires long-term treatment. *See* PTX 167 at GLD0223633-GLD0223634; PTX 172 at GLD0223641.

18. The administration of traditional doses of antibiotics, including doxycycline, can give rise to dose-dependent side effects that make long-term treatment undesirable. *See* PTX 167 at GLD00223635.

19. Those side effects include dizziness, phototoxicity (increased sensitivity to light), allergic reaction, hyperpigmentation, and gastrointestinal disturbances. *See* PTX 167 at GLD0223635; PTX 172 at GLD0223647.

20. Long-term use of traditional doses of antibiotics can lead to the development of antibiotic-resistant organisms. *See* PTX 167 at GLD0223635, GLD00223637.

21. Long-term antibiotic use can lead to the overgrowth of undesirable organisms such as yeasts. *See* PTX 167 at GLD00223637.

22. During the 1980s, many dermatologists became increasingly uncomfortable with the widespread use of antibiotic dosages of tetracyclines for the treatment of dermatological disorders because of the possibility that such use would lead to the evolution and proliferation of tetracycline-resistant bacteria. *See, e.g.*, PTX 167 at GLD0223637.

23. Antibiotic resistance has adverse effects because it means that known antibiotics may be rendered ineffective to treat many common infections at a population level. *See* PTX 167 at GLD00223637-GLD00223638.

24. The evolution and proliferation of resistant bacteria could lead to an epidemic of infection untreatable with known antibiotics. *See* PTX 167 at GLD00223637.

25. Antibiotic resistance may lead to increased susceptibility of individual patients to infections. *See* PTX 167 at GLD00223637.

26. Between 1999 and 2000, CollaGenex Pharmaceuticals, Inc. ("CollaGenex") successfully discovered that oral administration of low doses of doxycycline could be used to treat acne and rosacea while minimizing side effects common to long term administration of traditional antibiotic doses. *See* PTX 218 at GLD0001788.

27. CollaGenex discovered that Periostat® – a 20 mg doxycycline product indicated for the treatment of periodontitis – could be used as a twice-daily treatment for rosacea. *See* PTX 218 at GLD0001788.

28. Nevertheless, the use of Periostat® had the disadvantage of requiring twice-daily dosing, which is less convenient than a once-daily medication for patients with chronic medical conditions, such as rosacea, and may lead to issues of patient compliance with the prescribed dosing regime. *See* PTX 1 at GLD0000048, 1:64-2:4.

III. ORACEA

29. CollaGenex enlisted Shire Laboratories, Inc. ("Shire") to attempt to develop a once-daily formulation of Periostat® that would, among other things, help improve patient compliance while maintaining efficacy and avoiding unwanted side effects. *See, e.g.*, PTX 218 at GLD0001788; PTX 220 at GLD0001962; PTX 1 at GLD0000048, 2:1-16.

30. In 2003, CollaGenex first clinically tested the 30 mg immediate release ("IR"), 10 mg delayed release ("DR") once-daily doxycycline formulation developed by Shire. *See, e.g.*, PTX 218 at GLD0001788.

31. In May 2006, the FDA approved this 30 mg IR, 10 mg DR formulation for treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients, under the brand name Oracea®. *See* PTX 216; PTX 19 at 300, ¶ 17.

32. The Chang '532 patent and the Chang '740 patent (collectively, "the Chang patents") cover the commercial formulation for Oracea®. *See, e.g.*, Augsburger Dep. Tr. 12:10-12.

33. Oracea® contains an amount of doxycycline that, when administered once daily, will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml. *See* PTX 225 at GLD0005839-40; PTX 201 at GLD0287575.

34. Oracea® contains an amount of doxycycline that, when administered once daily, will give steady state blood levels of doxycycline of between 0.3 μg/ml to 0.8 μg/ml. *See* PTX 225 at GLD0005839-40; PTX 201 at GLD0287575.

IV. THE CHANG PATENTS

A. Amneal Infringes The Asserted Claims Of The Chang Patents

35. Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals Co. (I) PVT. Ltd. (collectively, "Amneal" or "Defendants") have infringed, either literally or under the doctrine of equivalents, any of Claims 1-8, 15-21 of the Chang '532 patent by submitting ANDA No. 203-278 seeking approval to market a generic version of Oracea® ("Amneal's Generic Product") prior to the expiration of the Chang '532 patent. *See* 35 U.S.C. § 271(e)(2)(A); *Yamanouchi Pharm. Co. v. Danbury Pharm., Inc.*, 231 F.3d 1339, 1346 (Fed. Cir. 2000).

36. Amneal will infringe, either literally or under the doctrine of equivalents, any of Claims 1-8, 15-21 of the Chang '532 patent if it makes, uses, offers to sell, sells and/or imports its Generic Product prior to the expiration of the Chang '532 patent.

37. Amneal will induce physicians, other healthcare professionals, caregivers or patients to infringe any of Claims 1-8, 15-21 of the Chang '532 patent.

38. Amneal will contribute to the infringement of any of Claims 1-8, 15-21 of the Chang '532 patent.

39. Amneal has infringed, either literally or under the doctrine of equivalents, any of Claims 1, 2, 6-15, 19-22 of the Chang '740 patent by submitting ANDA No. 203-278 seeking approval to market its Generic Product prior to the expiration of the Chang '740 patent. *See* 35 U.S.C. § 271(e)(2)(A); *Yamanouchi Pharm.*, 231 F.3d at 1346.

40. Amneal will infringe, either literally or under the doctrine of equivalents, any of Claims 1, 2, 6-15, 19-22 of the Chang '740 patent if it makes, uses, offers to sell, sells and/or imports its Generic Product prior to the expiration of the Chang '740 patent.

41. Amneal will induce physicians, other healthcare professionals, caregivers or patients to infringe any of Claims 1, 2, 6-15, 19-22 of the Chang '740 patent.

42. Amneal will contribute to the infringement of any of Claims 1, 2, 6-15, 19-22 of the Chang '740 patent.

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B. Amneal Cannot Prove That The Asserted Claims Of The Chang Patents Are Invalid

61. Amneal cannot prove by clear and convincing evidence that any of the asserted claims of the Chang patents are invalid as anticipated under 35 U.S.C. § 102.

62. Amneal cannot prove by clear and convincing evidence that any of the asserted claims of the Chang patents would have been obvious to a person of ordinary skill in the art under 35 U.S.C. § 103.

63. A person of ordinary skill in the field of the invention of the Chang patents would have education and experience in drug delivery and formulation. In this field, education and experience levels may vary between persons of ordinary skill, with some persons holding a Bachelor's degree with many years of experience and others holding higher degrees but having less work experience. Through education and/or experience, a person of ordinary skill would have knowledge and skill relating to the use, function and formulation of pharmaceutical excipients; knowledge and training regarding the equipment, processes and techniques used to analyze and test formulation materials; and an understanding of pharmacokinetic principles and how they relate to drug development.

64. The Chang patents have an earliest filing date of April 7, 2003, and the subject matter of the claims of the Chang patents was conceived and reduced to practice at least as of that date. PTX 1 at GLD00000041, GLD00000055; PTX 2 at GLD0280026.

1. The Chang Patents Are Novel And Non-Obvious

65. Amneal cannot prove by clear and convincing evidence that any one of the alleged prior art references relied on by Amneal (1) discloses each and every element, either expressly or inherently, of any asserted claim of the Chang patents, and (2) does so in a way that

would have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation as of the time of invention.

66. Amneal cannot prove by clear and convincing evidence that any of the alleged prior art references relied on by Amneal, either alone or in combination, would have rendered the subject matter of any asserted claim of the Chang patents obvious to a person of ordinary skill in the art at the time of invention.

67. Amneal cannot prove by clear and convincing evidence that any of the alleged prior art references relied on by Amneal, either alone or in combination, would have given a person of ordinary skill in the art as of the time of invention a reasonable expectation of success in obtaining the inventions claimed in any of the asserted claims of the Chang patents.

68. Amneal cannot prove by clear and convincing evidence that a person of ordinary skill in the art as of the time of invention would have had any reason or motivation to combine any of the alleged prior art references relied on by Amneal to obtain the inventions claimed in any of the asserted claims of the Chang patents.

a. The Ashley CR References Do Not Anticipate Or Render Obvious The Asserted Claims Of The Chang Patents

69. Amneal cannot prove by clear and convincing evidence that any one of the following three references (collectively, "the *Ashley CR References*") (1) discloses each and every element, either expressly or inherently, of any asserted claim of the Chang patents, and (2) does so in a way that would have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation as of the time of invention. *See, e.g.*, PTX 19 at 314, ¶¶ 255-262.

- U.S. Provisional Patent Application No. 60/281,854 ("the *Ashley '854 application*") (DTX 1030)[3]
- PCT Patent Application No. WO 02/083106 ("the *Ashley '106 publication*") (DTX 1039)
- U.S. Patent Application No. 10/474,240 ("the *Ashley '240 application*") (DTX 1003), published as U.S. Application Pub. No. 2004/0115261 ("the *Ashley '261 publication*").

70. Amneal cannot prove by clear and convincing evidence that any of the *Ashley CR References*, either alone or in combination, would have rendered the subject matter of any asserted claim of the Chang patents obvious to a person of ordinary skill in the art at the time of invention. *See, e.g.*, PTX 19 at 314, ¶¶ 255-262.

71. Amneal cannot prove by clear and convincing evidence that any of the *Ashley CR References*, either alone or in combination, would have given a person of ordinary skill in the art as of the time of invention a reasonable expectation of success in obtaining the inventions claimed in any of the asserted claims of the Chang patents.

72. Amneal cannot prove by clear and convincing evidence that a person of ordinary skill in the art as of the time of invention would have had a motivation to combine any of the *Ashley CR References* to obtain the inventions claimed in any of the asserted claims of the Chang patents.

73. Amneal cannot prove by clear and convincing evidence that any of the *Ashley CR References* disclose, teach or suggest the formulations claimed in any of the asserted claims of the Chang patents.

74. Amneal cannot prove by clear and convincing evidence that any of the *Ashley CR References* disclose, teach or suggest that the formulations claimed in the Chang patents will

[3] Amneal has not asserted that the *Ashley '854 application* alone anticipates the Chang patents.

give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml.

75. Amneal cannot prove by clear and convincing evidence that the *Ashley CR References* provide a person of ordinary skill in the art at the time of the Chang patents with a reasonable expectation that the claimed 30 mg IR, 10 mg DR formulations of the Chang patents would be successful to meet the Chang inventors' therapeutic goal of obtaining a once-daily doxycycline formulation that maintains blood levels sufficient to achieve therapeutic effect comparable to twice-daily Periostat®, while remaining well below blood levels linked to side effects of antibiotic doxycycline formulations.

76. The *Ashley CR References* do not disclose any examples of any actual formulations. *See, e.g.*, Augsburger Dep. Tr. at 45:6-10; PTX 19 at 314, ¶ 259.

77. The inventor of the *Ashley CR References* did not make any formulations of doxycycline. *See, e.g.*, Augsburger Dep. Tr. at 45:6-10; PTX 19 at 314, ¶ 260.

78. The *Ashley CR References* do not disclose, teach or suggest any compositions that contain only an IR portion and a DR portion. *See, e.g.*, PTX 19 at 314, ¶ 261; Augsburger Dep. Tr. at 74:8-75:7.

79. The *Ashley CR References* do not disclose, teach or suggest any composition that contains a 30 mg IR doxycycline component. *See* PTX 19 at 314, ¶ 262.

80. The *Ashley CR References* do not disclose, teach or suggest any composition that contains a 10 mg DR doxycycline component. *See* PTX 19 at 314, ¶ 262.

81. The *Ashley CR References* do not disclose, teach or suggest any composition that consists of an IR portion containing 30 mg doxycycline, and a DR portion containing 10 mg doxycycline. *See, e.g.*, PTX 19 at 314, ¶¶ 256, 262; Augsburger Dep. Tr. at 45:6-46:4.

82. The *Ashley CR References* do not disclose, teach, or suggest a 75:25 ratio of IR to DR portions of doxycycline. *See* PTX 19 at 314, ¶ 256.

83. Amneal cannot show by clear and convincing evidence that the 30 mg IR, 10 mg DR doxycycline ratio is not critical or central to the operation of the claimed invention of the Chang patents.

84. The different 40 mg IR/DR doxycycline ratios between the range of 40 mg IR, 0 mg DR and 0 mg IR, 40 mg DR operate differently in terms of pharmacokinetic performance, which can impact therapeutic effect and safety.

85. Amneal cannot show by clear and convincing evidence that the confidential data upon which their expert witness Dr. Bergstrom bases his pharmacokinetic modeling set forth by Amneal in this case is prior art.

86. The *Ashley CR References* do not disclose, teach or suggest a once daily formulation of doxycycline as claimed in the Chang patents that could be used for a method of treating rosacea.

87. The *Ashley CR References* do not disclose, teach or suggest the use of any doxycycline formulation for the treatment of rosacea.

88. The *Ashley CR References* teach away from the inventions of the Chang patents because the *Ashley CR References* require formulations that release drug from the dosage form at a substantially constant rate for a period of 6-24 hours, preferably for a period of 12-24 hours.

89. The *Ashley '106 publication* is disclosed and incorporated by reference in the Chang patents. *See* PTX 1 at GLD0000049, 3:40-43; PTX 2 at GLD0280038, 3:40-43.

90. The *Ashley '106 publication* was considered by the United States Patent and Trademark Office ("PTO") and was cited by the examiner during prosecution of both Chang

patents. *See* PTX 1 at GLD00000041; PTX 2 at GLD0280027; PTX 6 at GLD0280094; *see also* PTX 5 at GLD0001117.

91. The *Ashley '261 publication*, which is a U.S. publication of the *Ashley '240 application* was considered by the PTO and was cited by the examiner during the prosecution of both Chang patents. *See* PTX 1, GLD00000041; PTX 2 at GLD0280027.

92. The examiner allowed the claims of the Chang patents on the basis that the prior art does not teach or fairly suggest a dosage form consisting of a 30 mg IR portion and a 10 mg DR portion. *See* PTX 5 at GLD0001435-GLD0001437; PTX 6 at GLD0280262-GLD0280264.

93. Defendants have failed to show by clear and convincing evidence that the prosecution history of the *Ashley '240 application* constitutes prior art to either of the Chang patents. *See, e.g.*, Augsburger Dep. Tr. at 57:17-21.

b. The Ashley Method Of Use References Do Not Anticipate Or Render Obvious The Asserted Claims Of The Chang Patents

94. Amneal cannot prove by clear and convincing evidence that any one of the following two references (collectively, "the *Ashley Method of Use References*") (1) discloses each and every element, either expressly or inherently, of any asserted claim of the Chang patents, and (2) does so in a way that would have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation as of the time of invention.

- PCT Application No. WO 02/080932 ("the *Ashley '932 publication*") (DTX 1038)
- U.S. Patent No. 7,232,572 ("the *Ashley '572 patent*") (DTX 1165)

95. Amneal cannot prove by clear and convincing evidence that either of the *Ashley Method of Use References*, either alone or in combination, would have rendered the subject matter of any of the asserted claims of the Chang patents obvious to a person of ordinary skill in the art at the time of invention.

96. Amneal cannot prove by clear and convincing evidence that either of the *Ashley Method of Use References*, either alone or in combination, would have given a person of ordinary skill in the art as of the time of invention a reasonable expectation of success in obtaining the inventions claimed in any of the asserted claims of the Chang patents.

97. Amneal cannot prove by clear and convincing evidence that a person of ordinary skill in the art as of the time of invention would have had any reason or motivation to combine the *Ashley Method of Use References* to obtain the inventions claimed in any of the asserted claims of the Chang patents.

98. The *Ashley Method of Use References* do not disclose each and every element of any of the asserted claims of the Chang patents.

99. The *Ashley Method of Use References* do not disclose, teach or suggest any compositions that contain only an IR portion and a DR portion. *See* PTX 19 at 314, ¶¶ 256, 263.

100. The *Ashley Method of Use References* do not disclose, teach or suggest any composition that contains a 30 mg IR component. *See* Augsburger Dep. Tr. at 43:25-46:4; PTX 19 at 314, ¶ 264.

101. The *Ashley Method of Use References* do not disclose, teach or suggest any composition that contains a 10 mg DR component. *See* Augsburger Dep. Tr. at 43:25-46:4; PTX 19 at 314, ¶ 264.

102. The *Ashley Method of Use References* do not disclose, teach or suggest any composition that consists of an IR portion containing 30 mg doxycycline, and a DR portion containing 10 mg doxycycline. *See* Augsburger Dep. Tr. at 43:25-46:4; PTX 19 at 314, ¶ 264.

103. The *Ashley Method of Use References* do not disclose, teach, or suggest a 75:25 ratio of IR to DR portions of doxycycline. *See* PTX 19 at 314, ¶ 264.

104. Amneal cannot prove by clear and convincing evidence that the *Ashley Method of Use References* provide a person of ordinary skill in the art at the time of the Chang patents with a reasonable expectation that the claimed 30 mg IR, 10 mg DR formulations of the Chang patents would be successful to meet the Chang inventors' therapeutic goal of obtaining a once-daily doxycycline formulation that maintains blood levels sufficient to achieve therapeutic effect comparable to twice-daily Periostat®, while remaining well below blood levels linked to side effects of antibiotic doxycycline formulations.

105. Amneal cannot show by clear and convincing evidence that the 30 mg IR, 10 mg DR doxycycline ratio is not critical or central to the operation of the claimed invention of the Chang patents.

106. The different 40 mg IR/DR doxycycline ratios between the range of 40 mg IR, 0 mg DR and 0 mg IR, 40 mg DR operate differently in terms of pharmacokinetic performance, which can impact therapeutic effect and safety.

107. Amneal cannot show by clear and convincing evidence that the data upon which their expert witness Dr. Bergstrom bases his pharmacokinetic modeling set forth by Amneal in this case is prior art.

108. To the extent the *Ashley Method of Use References* incorporate by reference the *Ashley '854 application*, the *Ashley Method of Use References* teach away from the inventions of the Chang patents because the *Ashley Method of Use References* require formulations that release drug from the dosage form at a substantially constant rate for a period of 6-24 hours, preferably for a period of 12-24 hours.

109. The *Ashley '932 publication* is disclosed in the Chang '740 patent. *See* PTX 2 at GLD0280027.

110. The *Ashley '572 patent* is disclosed in the Chang patents. *See* PTX 1 at GLD0000041; PTX 2 at GLD0280027.

c. The Ashley CR References In Combination With The Ashley Method of Use References Do Not Render Obvious The Asserted Claims Of The Chang Patents

111. Amneal cannot prove by clear and convincing evidence that the *Ashley Method of Use References* or the *Ashley CR References* (collectively, "the *Ashley References*"), either alone or in any possible combination, would have rendered the subject matter of any of the asserted claims of the Chang patents obvious to a person of ordinary skill in the art at the time of invention.

112. Amneal cannot prove by clear and convincing evidence that the *Ashley References*, either alone or in any possible combination, would have given a person of ordinary skill in the art as of the time of invention a reasonable expectation of success in obtaining the inventions claimed in any of the asserted claims of the Chang patents.

113. Amneal cannot prove by clear and convincing evidence that a person of ordinary skill in the art as of the time of invention would have had any reason or motivation to combine the *Ashley References* to obtain the inventions claimed in any of the asserted claims of the Chang patents.

114. Amneal cannot prove by clear and convincing evidence that the *Ashley References* provide a person of ordinary skill in the art at the time of the Chang patents with a reasonable expectation that the claimed 30 mg IR, 10 mg DR formulations of the Chang patents would be successful to meet the Chang inventors' therapeutic goal of obtaining a once-daily doxycycline formulation that maintains blood levels sufficient to achieve therapeutic effect comparable to twice-daily Periostat®, while remaining well below blood levels linked to side effects of antibiotic doxycycline formulations.

115. Of the *Ashley References*, the *Ashley '932 publication*, the *Ashley '106 publication*, the *Ashley '572 patent*, and the *Ashley '854 application* were before the Court in *Mylan Pharms., Inc. v. Galderma Laboratories Inc. et al.*, No. 10-892 (D. Del.) ("the *Mylan* action") as alleged prior art asserted against the Chang '532 patent. *See* PTX 19 at 314 n.7 & n.8. Following trial in the *Mylan* action, the Court found that the Chang '532 patent was not anticipated or rendered obvious by the *Ashley '932 publication* or the *Ashley '854 application*, which it is incorporated into the *Ashley '932 publication*. *See id.* at 332-33.

116. Following an appeal by Mylan, joined in by several other generic drug companies, the Federal Circuit affirmed in whole this Court's rulings regarding the validity of the Chang '532 patent, including its rulings that the *Ashley '932 publication* or the *Ashley '854 application* do not anticipate or render obvious the Chang '532 patent. PTX 20 at 6, 9.

d. The Ashley References in Combination With The Sheth '748 patent Do Not Render Obvious The Asserted Claims Of The Chang Patents

117. Amneal cannot prove by clear and convincing evidence that U.S. Patent No. 5,348,748 ("the *Sheth '748 patent*") (DTX 1040), either alone or in combination with any of the *Ashley References*, would have rendered the subject matter of any asserted claim of the Chang patents obvious to a person of ordinary skill in the art at the time of invention.

118. Amneal cannot prove by clear and convincing evidence that the *Sheth '748 patent*, either alone or in combination with any of the *Ashley References*, would have given a person of ordinary skill in the art as of the time of invention a reasonable expectation of success in obtaining the inventions claimed in any of the asserted claims of the Chang patents.

119. None of the *Ashley References* in view of the *Sheth '748 patent* provide any teaching, disclosure or suggestion (alone or in combination) that render obvious the inventions of any of the asserted claims of the Chang patents.

120. Amneal cannot prove by clear and convincing evidence that a person of ordinary skill in the art as of the time of invention would have had any reason or motivation to combine the *Sheth '748 patent* with any of the *Ashley References* in order to obtain the inventions claimed in any of the asserted claims of the Chang patents.

121. None of the *Ashley References* provide any reason or motivation to combine its teachings with the *Sheth '748 patent.*

122. The *Sheth '748 patent* provides no reason or motivation to combine its teachings with any of the *Ashley References.*

123. Amneal cannot prove by clear and convincing evidence that the *Sheth '748 patent* discloses, teaches or suggests any formulations claimed in the asserted claims of the Chang patents.

124. The *Sheth '748 patent* does not disclose, teach or suggest any composition that contains a 30 mg IR component of doxycycline.

125. The *Sheth '748 patent* does not disclose, teach or suggest any composition that contains a 10 mg DR component of doxycycline.

126. The *Sheth '748 patent* does not disclose, teach or suggest any compositions that contain only an IR portion and a DR portion.

127. The *Sheth '748 patent* does not disclose, teach or suggest any composition that consists of an IR portion containing 30 mg doxycycline, and a DR portion containing 10 mg doxycycline.

128. The *Sheth '748 patent* does not disclose, teach or suggest any method of treating rosacea.

129. The *Sheth '748 patent* discloses only formulations using minocycline, not doxycycline. *See* Augsburger Dep. Tr. at 83:13-15, 180:18-23, 185:6-12.

130. Minocycline and doxycycline are not interchangeable. *See, e.g.*, PTX 174 at GLD0279737-GLD0279738.

131. Minocycline and doxycycline have different physical properties. *See* PTX 195 at 356.

132. Minocycline and doxycycline have different chemical properties. *See* PTX 195 at 356.

133. Minocycline and doxycycline have different pharmacokinetic properties. *See* PTX 195 at 356.

134. Minocycline and doxycycline are structurally different in three different locations. *See* PTX 195 at 356.

135. The *Sheth '748 patent* provides formulations of therapeutic antibiotic dosage levels of minocycline for up to about twenty-four hours. *See, e.g.*, DTX 1040 at 6:26-34.

136. The *Sheth '748 patent* teaches away from the invention of the Chang patents because the *Sheth '748 patent* discloses and claims formulations in which both components are independently therapeutic and traditional antibiotic doses. *See, e.g.*, DTX 1040 at 4:40-49, 4:58-5:10, 6:26-34, 7:49-59.

137. The *Sheth '748 patent* teaches away from the invention of the Chang patents because the *Sheth '748 patent* does not disclose any formulations with maximum or ceiling concentrations, whereas the asserted claims of the Chang patents require formulations that have steady state blood levels of doxycycline of a maximum of 1.0 μg/ml.

138. The *Sheth '748 patent* teaches away from the invention of the Chang patents because the *Sheth '748 patent* describes formulations including a "secondary loading portion" of minocycline with a "blended polymer" coating composed of both pH-sensitive and water-soluble polymers, which forms pores when the water-soluble polymer dissolves immediately in the stomach, and immediately begins slow, sustained release of minocycline in the stomach through the pores. *See, e.g.*, DTX 1040 at 3:48-58, 4:67-5:10, 8:53-62, 10:56-67, 14:36-41, 15:7-12, 15:48-53, 16:3-18, 16:43-52. In contrast, the asserted claims of the Chang patents require a 10 mg DR doxycycline portion, which substantially precludes drug release in the acidic environment of the stomach. PTX 1 at GLD0000051, 7:47-49, Figs. 1-3; PTX 2 at GLD0280040, 7:47-49, Figs. 1-3.

e. The Periostat® References In View of the Sheth '748 Patent And The 2001 Annual Report Do Not Render Obvious The Claims Of The Chang Patents

139. Amneal cannot prove by clear and convincing evidence that the following references (collectively, "the *Periostat® References*"), either alone or in combination with the *Sheth '748 patent* (DTX 1040) and the 2001 Annual Report for CollaGenex Pharmaceuticals, Inc. ("the *2001 Annual Report*") (DTX 1294), would have rendered the subject matter of any of the asserted claims of the Chang patents obvious to a person of ordinary skill in the art at the time of invention.

- FDA Approval Package for Periostat® Capsules ("*Periostat® Approval Package*") (DTX 1145)
- Commercially available Periostat® Capsules product

140. Amneal cannot prove by clear and convincing evidence that the *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the *2001 Annual Report*, would have given a person of ordinary skill in the art as of the time of invention a

reasonable expectation of success in obtaining the inventions claimed in any of the asserted claims of the Chang patents.

141. Amneal cannot prove by clear and convincing evidence that a person of ordinary skill in the art as of the time of invention would have had any reason or motivation to combine the *Periostat® References* with the *Sheth '748 patent* and the *2001 Annual Report* in order to obtain the inventions claimed in any of the asserted claims of the Chang patents.

142. Amneal cannot prove by clear and convincing evidence that the *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the *2001 Annual Report*, disclose, teach or suggest any formulation claimed in the asserted claims the Chang patents.

143. Amneal cannot prove by clear and convincing evidence that the *Periostat® Approval Package* is prior art to the Chang patents.

144. Amneal cannot prove by clear and convincing evidence that the *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the *2001 Annual Report*, disclose, teach or suggest that the formulations claimed in the Chang patents will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml.

145. Amneal cannot prove by clear and convincing evidence that the *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the *2001 Annual Report*, provide a person of ordinary skill in the art at the time of the Chang patents with a reasonable expectation that the claimed 30 mg IR, 10 mg DR formulations of the Chang patents would be successful to meet the Chang inventors' therapeutic goal of obtaining a once-daily doxycycline formulation that maintains blood levels sufficient to achieve therapeutic effect

comparable to twice-daily Periostat®, while remaining well below blood levels linked to side effects of antibiotic doxycycline formulations.

146. Amneal cannot prove by clear and convincing evidence that the *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the *2001 Annual Report*, disclose, teach or suggest any doxycycline formulation containing only an IR portion and a DR portion.

147. The *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the 2001 Annual Report, do not disclose, teach or suggest any composition that consists of an IR portion containing 30 mg doxycycline.

148. The *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the 2001 Annual Report, do not disclose, teach or suggest any composition that consists of a DR portion of 10 mg doxycycline.

149. The *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the 2001 Annual Report, do not disclose, teach or suggest any composition that consists of an IR portion containing 30 mg doxycycline and a DR portion containing 10 mg doxycycline.

150. As of the time of invention of the Chang patents, Periostat® was a 20 mg immediate release formulation of doxycycline hyclate, indicated for twice-daily administration for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis. PTX203 at GLD0177992; PTX 204 at GLD0230257.

151. The *Periostat® References*, either alone or in combination with the *Sheth '748 patent* and the 2001 Annual Report, do not disclose, teach or suggest any methods of treating rosacea.

152. None of the *Periostat® References* (alone or in combination) in view of the *Sheth '748 patent* provide any teaching, disclosure or suggestion that would anticipate or render obvious the inventions of the Chang patents.

153. None of the *Periostat® References* (alone or in combination) in view of the 2001 Annual Report provide any teaching, disclosure or suggestion that would anticipate or render obvious the inventions of the Chang patents.

154. The *Periostat® References* do not provide any reason or motivation to combine any of their teachings with the *Sheth '748 patent* or the *2001 Annual Report*.

155. Neither the *Sheth '748 patent* nor the *2001 Annual Report* provides any reason or motivation to combine its teachings with any of the teachings of the *Periostat® References*.

2. Objective Indicia Of Non-Obviousness

a. Nexus

156. Oracea® is the commercial embodiment of the Chang '532 patent.

157. The asserted claims of the Chang '532 patent cover Oracea®.

158. Oracea® is the commercial embodiment of the Chang '740 patent.

159. The asserted claims of the Chang '740 patent cover Oracea®.

160. Oracea® is a commercial success. *See* PTX 258 at GLD0224462; PTX 255 at GLD0107960-GLD0107962; PTX 257 at GLD0178900; PTX 261 at GLD0279459, PTX 266 at GLD0287387-GLD0287389.

161. Oracea® has generated significant sales in the relevant market.

162. There is a nexus between the commercial success of Oracea® and the inventions of the asserted claims of the Chang '532 patent.

163. There is a nexus between the commercial success of Oracea® and the inventions of the asserted claims of the Chang '740 patent.

164. Amneal cannot rebut Galderma's *prima facie* showing of nexus by providing evidence that the commercial success of Oracea® is due to factors that are not related to the inventions of the asserted claims of the Chang patents.

165. The Ashley '572 patent is not a "blocking patent" because, *inter alia*, the '572 patent did not issue until several years after the effective filing date for the Chang patents. *See* PTX 1 at GLD00000041, GLD00000055; PTX 2 at GLD0280026; DTX 1002.

b. Long-Felt, Unmet Need

166. Prior to the invention of the Chang patents, marketed as Oracea®, there was a long-felt, unmet need for a once-daily oral formulation of doxycycline to treat symptoms of rosacea without subjecting patients to undesired side effects associated with long-term administration of antibiotic doses of doxycycline. *See* PTX 172, at GLD0223641; PTX 19 at 316, ¶ 293.

167. Once-daily Oracea® met the long-felt need for a once-daily oral formulation of doxycycline to treat the symptoms of rosacea without subjecting patients to undesired side effects associated with long-term administration of antibiotic doses of doxycycline. *See* PTX 19 at 316, ¶¶ 292-293.

168. Prior to the invention of the Chang patents, marketed as Oracea®, there was a long-felt need for a formulation that permitted once-daily administration of doxycycline in order to increase patient compliance. *See* PTX 19 at 316, ¶ 293.

169. The benefits of a once-daily formulation over twice-daily antibiotic dosing include, among other things, improved patient compliance. *See* Augsburger Dep. Tr. at 228:18-23.

170. Patients prefer the convenience of once-daily dosing formulations over formulations that require administration twice-daily or even more frequently. *See* Gilmore Dep. Tr. at 101:9-102:2.

171. Patient compliance is particularly important for longer treatment periods, as is generally required in treating rosacea. See PTX 167 at GLD0223637-GLD0223638.

172. Once-daily Oracea® met the long-felt need for a formulation that permitted once-daily administration of doxycycline in order to increase patient compliance.

173. Prior to the invention of the Chang patents, marketed as Oracea®, there existed a long-felt need for a once-daily formulation of twice-daily Periostat®. *See* Augsburger Dep. Tr. at 228:11-17.

174. Patients are more likely to comply with a once-daily dosing regimen like that of Oracea® than with a twice-daily regimen like Periostat®. *See* PTX 167 at GLD0223637; PTX 194 at GLD0279468; Augsburger Dep. Tr. at 28:14-29:3, 228:18-23.

175. Once-daily Oracea® met the long-felt need for a once-daily formulation of twice-daily Periostat®.

176. Prior to the invention of the Chang patents, marketed as Oracea®, there was a long-felt, unmet need by doctors and their patients for a convenient method of treating rosacea with doxycycline that permits once-daily administration to increase patient compliance with that treatment, while still avoiding the side effects associated with the long-term use of traditional antibiotic doses. *See* PTX 1 at GLD0000048, 2:1-16.

177. Oracea®, a 30 mg IR, 10 mg DR formulation, is as effective as 100 mg doxycycline in treating the symptoms of rosacea, but it has significantly fewer side effects. *See* PTX 180 at GLD0223740.

178. Once-daily Oracea® met the long-felt need for a convenient method of treating rosacea with doxycycline that permits once-daily administration to increase patient compliance with that treatment, while still avoiding the side effects associated with the long-term use of traditional antibiotic doses.

c. Failure Of Others

179. Persons of ordinary skill in the art attempted to develop once-daily doxycycline formulations that would be therapeutically effective while avoiding blood levels linked to antibacterial side effects, and failed in doing so. *See, e.g.*, PTX 241 at GLD0227794; PTX 242 at GLD0272730; PTX 243 at GLD0227342-GLD0227343; PTX 19 at 315-16, ¶¶ 283-85.

180. In 1998, CollaGenex attempted to develop a once daily formulation of doxycycline in partnership with FH Faulding & Co. Limited ("Faulding"). Faulding formulated three 40 mg doxycycline drug products intended for once-daily administration, each of which failed. *See, e.g.*, PTX 241 at GLD0227794; PTX 242 at GLD0272730; PTX 243 at GLD0227342; PTX 19 at 315-16, ¶¶ 283-85.

181. Faulding attempted to develop a once-daily 40 mg doxycycline formulation using water swellable and water insoluble polymers in the bead coat in conjunction with different organic acids in an attempt to influence the solubility and absorption of doxycycline. *See* PTX 241 at GLD0227795; PTX 242 at GLD0272730.

182. Doxycycline formulations developed by Faulding for CollaGenex were not successful because the bioavailability of Faulding's formulations was significantly compromised.

See, *e.g.*, PTX 241 at GLD0227794; PTX 242 at GLD0272730; PTX 243 at GLD0227342; PTX 244 at GLD0274711-GLD0274712; PTX 19 at 315-16, ¶¶ 283-85.

183. Formulations developed by Faulding were not successful in achieving once-daily administration of doxycycline that, for as many patients as possible, would be therapeutically effective while avoiding blood levels linked to antibacterial side effects and avoiding gastrointestinal side effects due to unabsorbed doxycycline in the GI tract. *See* PTX 242 at GLD0272730; PTX 241 at GLD0227794, GLD0227799-GLD0227800; PTX 243 at GLD0227342; PTX 244 at GLD0274711-GLD0274712; DTX 1294 at 15; PTX 19 at 315-16, ¶¶ 283-285.

d. Unexpected Results

184. Surprisingly, a once-daily dose of Oracea® is as effective as a once-daily dose of 100 mg doxycycline in treating the symptoms of rosacea, while having fewer side effects. *See* PTX 180 at GLD0223740.

185. A once-daily 30 mg IR, 10 mg DR doxycycline formulation as claimed in the Chang patents would not have been expected to meet the Chang inventors' goal of providing blood levels sufficient for therapeutic efficacy comparable to twice-daily Periostat®, while avoiding high blood levels linked to antibacterial side effects.

e. Copying

186. Five generic companies – Mylan, Impax Laboratories, Inc., Lupin Limited, Sandoz Inc., and Amneal – seek FDA approval to market generic versions of Oracea® in the United States. *See* PTX 289 at GLD0279996; PTX 290 at GLD0279944, PTX 291 at GLD0279982, PTX 292 at 1; PTX 293 at 1, 3; PTX 10; PTX 11.

187. Despite widespread generic availability of multiple immediate-release and controlled release formulations of doxycycline, five generic drug companies, including Amneal, have sought to market generic formulations of Oracea®.

188. Despite widespread generic availability of multiple unpatented immediate-release and controlled release formulations of doxycycline, five generic drug companies, including Amneal, have sought to market generic formulations of Oracea®.

189. Amneal's Generic Product does not differ from the formulation of the asserted claims of the Chang patents. *Compare* PTX 208 at AMORA_00000026-AMORA_00000027, *with* PTX 1 at GLD0000053-GLD0000054, Claims 1-8, 15-21, *and* PTX 2 at GLD0280042, Claims 1, 2, 6-15, 19-22.

190. In developing a generic product designed to be bioequivalent to Oracea®, Amneal did not consider and made no attempt to manufacture a once-daily product that does not contain a 30 mg IR, 10 mg DR dose of doxycycline. *See* Kumar Dep. Tr. at 142:18-144:9; Edwards Dep. Tr. at 94:12-20.

191. Amneal believes that its proposed generic Oracea® product is bioequivalent to Oracea®. *See* Edwards Dep. Tr. at 118:4-7; PTX 15 at Response No. 29.

192. Generic doxycycline is commercially available in at least 50 mg, 75 mg, 100 mg, and 150 mg dosage forms.

193. Several immediate-release and once daily antibiotic dosage forms of doxycycline are available as branded and generic drugs.

f. Industry Acceptance

194. Oracea® has gained wide acceptance among physicians and health care payers, as is demonstrated by the substantial and growing sales and prescriptions of Oracea®, and the wide

coverage of Oracea® on the formularies of commercial health care plans. *See infra* at ¶¶ 189-235.

g. Commercial Success

195. Oracea is a commercial success. *See* PTX 19 at 316, ¶ 288.

(i) Oracea® Sales

196. According to sales data maintained by Wolters-Kluwer Health, Inc. ("WKH"), gross sales of Oracea® for the period of July 2006 through December 2006 were approximately $13.5 million. *See* PTX 258 at GLD0224474.

197. According to sales data maintained by WKH, gross sales of Oracea® for the period of January 2007 through December 2007 were approximately $68.2 million. *See* PTX 258 at GLD0224474; PTX 267 at GLD0279431.

198. [redacted]

REDACTED

199. According to sales data maintained by WKH, gross sales of Oracea® for the period of January 2008 through December 2008 were approximately $105.1 million. *See* PTX 258 at GLD0224462.

200. [redacted]

REDACTED

201. According to sales data maintained by WKH, gross sales of Oracea® for the period of January 2009 through December 2009 were approximately $183.1 million. *See* PTX 258 at GLD0224462; PTX 145.

202. [redacted]

REDACTED

203. According to sales data maintained by WKH, gross sales of Oracea® for the period of January 2010 through December 2010 were approximately $291.4 million. *See* PTX 145.

204. [redacted]

205. According to sales data maintained by WKH, gross sales of Oracea® for the period of January 2011 through December 2011 were approximately $342.0 million. *See* PTX 145.

206. [redacted]

207. According to sales data maintained by WKH, gross sales of Oracea® for the period of January 2012 through December 2012 were approximately $406.5 million. *See* PTX 145.

208. [redacted]

209. According to sales data maintained by WKH, Oracea® has generated over $1.409 billion in gross sales in the United States, from launch in July 2006 through the end of December 2012. *See* PTX 258 at GLD0224462; PTX 145.

210. [redacted]

211. Annual gross sales of Oracea® have increased every year since launch through 2012. *See* PTX 258 at GLD0224462; PTX 145.

212. [redacted]

[redacted]

[redacted]

(ii) Oracea® Prescriptions

213. Total prescriptions are the sum of new and refill prescriptions.

214. According to prescription data maintained by WKH, total prescriptions filled for Oracea® for the period of July 2006 through December 2006 were approximately 88,700. *See* PTX 258 at GLD0224462.

215. According to prescription data maintained by WKH, new prescriptions filled for Oracea® for the period of July 2006 through December 2006 were approximately 60,700. *See* PTX 258 at GLD0224468.

216. According to prescription data maintained by WKH, refill prescriptions filled for Oracea® for the period of July 2006 through December 2006 were approximately 28,000. *See* PTX 258 at GLD0224462, GLD0224468.

217. According to prescription data maintained by WKH, total prescriptions filled for Oracea® for the period of January 2007 through December 2007 were approximately 383,200. *See* PTX 258 at GLD0224462.

218. According to prescription data maintained by WKH, new prescriptions filled for Oracea® for the period of January 2007 through December 2007 were approximately 190,300. *See* PTX 258 at GLD0224468.

219. According to prescription data maintained by WKH, refill prescriptions filled for Oracea® for the period of January 2007 through December 2007 were approximately 192,900. *See* PTX 258 at GLD0224468.

220. According to prescription data maintained by WKH, total prescriptions filled for Oracea® for the period of January 2008 through December 2008 were approximately 478,600. *See* PTX 258 at GLD0224462.

221. According to prescription data maintained by WKH, new prescriptions filled for Oracea® for the period of January 2008 through December 2008 were approximately 211,200. *See* PTX 258 at GLD0224468.

222. According to prescription data maintained by WKH, refill prescriptions filled for Oracea® for the period of January 2008 through December 2008 were approximately 267,400. *See* PTX 258 at GLD0224462, GLD0224468.

223. According to prescription data maintained by WKH, total prescriptions filled for Oracea® for the period of January 2009 through December 2009 were approximately 588,300. *See* PTX 258 at GLD0224462; PTX 145.

224. According to prescription data maintained by WKH, new prescriptions filled for Oracea® for the period of January 2009 through December 2009 were approximately 265,900. *See* PTX 258 at GLD0224468; PTX 145.

225. According to prescription data maintained by WKH, refill prescriptions filled for Oracea® for the period of January 2009 through December 2009 were approximately 322,400. *See* PTX 258 at GLD0224462, GLD0224468; PTX 145.

226. According to prescription data maintained by WKH, total prescriptions filled for Oracea® for the period of January 2010 through December 2010 were approximately 724,000. *See* PTX 145.

227. According to prescription data maintained by WKH, new prescriptions filled for Oracea® for the period of January 2010 through December 2010 were approximately 299,500. *See* PTX 145.

228. According to prescription data maintained by WKH, refill prescriptions filled for Oracea® for the period of January 2010 through December 2010 were approximately 424,500. *See* PTX 145.

229. According to prescription data maintained by WKH, total prescriptions filled for Oracea® for the period of January 2011 through December 2011 were approximately 750,200. *See* PTX 145.

230. According to prescription data maintained by WKH, new prescriptions filled for Oracea® for the period of January 2011 through December 2011 were approximately 307,400. *See* PTX 145.

231. According to prescription data maintained by WKH, refill prescriptions filled for Oracea® for the period of January 2011 through December 2011 were approximately 442,800. *See* PTX 145.

232. According to prescription data maintained by WKH, total prescriptions filled for Oracea® for the period of January 2012 through December 2012 were approximately 822,000. *See* PTX 145.

233. According to prescription data maintained by WKH, new prescriptions filled for Oracea® for the period of January 2012 through December 2012 were approximately 333,400. *See* PTX 145.

234. According to prescription data maintained by WKH, refill prescriptions filled for Oracea® for the period of January 2012 through December 2012 were approximately 488,500. *See* PTX 145.

235. According to prescription data maintained by WKH, for the year ending December 2010, Oracea® is the most prescribed of all products that have been approved by the FDA for the treatment of rosacea. *See* PTX 268 at GLD0279520, GLD0279524.

236. According to prescription data maintained by WKH, for the year ending December 2010, Oracea® was the most-prescribed orally-administered branded pharmaceutical for treatment of rosacea by dermatologists. *See* PTX 268 at GLD0279520, GLD0279524.

237. According to prescription data maintained by WKH, total prescriptions for Oracea® have increased each year since launch. *See* PTX 258 at GLD0224462; PTX 145.

238. According to prescription data maintained by WKH, new prescriptions for Oracea® have increased each year since launch. *See* PTX 258 at GLD0224462; PTX 145.

239. According to prescription data maintained by WKH, refill prescriptions for Oracea® have increased each year since launch. *See* PTX 258 at GLD0224462; PTX 145.

(iii) Formulary Coverage Of Oracea®

240. According to data maintained by Fingertip Formulary, as of October 22, 2010, 0.3% of covered lives in commercial plans receive coverage for Oracea® as a Tier 1 drug product. *See* PTX 153.

241. According to data maintained by Fingertip Formulary, as of October 22, 2010, 23.4% of covered lives in commercial plans receive coverage for Oracea® as a Tier 2 drug product. *See* PTX 153.

242. According to data maintained by Fingertip Formulary, as of October 22, 2010, 66.4% of covered lives in commercial plans receive coverage for Oracea® as a Tier 3 drug product. *See* PTX 153.

C. Enforceability of the Chang Patents in Light of Amneal's Inequitable Conduct Allegations

243. Amneal cannot show by clear and convincing evidence that any of the asserted claims of the Chang patents is unenforceable on the grounds of alleged inequitable conduct.

244. Amneal cannot show by clear and convincing evidence that during the prosecution of the Chang patents before the United States Patent and Trademark Office ("PTO") the patentee both (1) withheld information with the specific intent to deceive the PTO, and (2) the allegedly withheld information was "but-for material."

245. Amneal cannot prove by clear and convincing evidence that REDACT acted with specific intent to deceive the PTO.

246. Amneal cannot prove by clear and convincing evidence that REDACTE [redacted] REDACTED

247. Amneal does not have any factual basis for its allegation that REDAC knew that the allegedly [redacted] was material or that she intentionally withheld it with intent to deceive the PTO.

248. REDAC has no recollection of whether she ever received or discussed REDAC [redacted]

249. Amneal cannot prove that an inference of specific intent to deceive the PTO is the single most reasonable inference able to be drawn from the evidence.

250. Amneal cannot prove by clear and convincing evidence that the allegedly [redacted] to either of the Chang patents.

251. Amneal cannot prove by clear and convincing evidence that the PTO would not have allowed any of the asserted claims of the Chang patents had it been aware of [redacted]

252. Based on the specification of the Chang patents, the PTO Examiner was well aware that the claimed [redacted]

37.

253. [redacted] demonstrate that the inventors were able to develop a formulation that achieved the objective stated in the specifications of the Chang patents, [redacted]

254. [redacted] supports patentability of the claimed inventions of the Chang patents because it demonstrates that the patentee successfully overcame the challenge [redacted]

255. Amneal cannot prove by clear and convincing evidence that [redacted] to the PTO constitutes an affirmative act of egregious misconduct.

256. [***Plaintiffs reserve the right to supplement their Issues of Fact to be Litigated at Trial with respect to Defendants' allegations regarding inequitable conduct, for which discovery requested by Defendants is presently ongoing.***]

D. Enforceability With Respect To Amneal Of The Chang '740 Patent In Light of Amneal's Unclean Hands Allegations

257. Amneal cannot show that any of the asserted claims of the Chang '740 patent are unenforceable with respect to Amneal on the grounds of alleged unclean hands.

258. Amneal cannot show by clear and convincing evidence that REDACTED REDACTED (1) engaged in conduct involving fraud, deceit, unconscionability, or bad faith, (2) that REDACTED alleged conduct had an immediate and necessary relationship to the equity sought, or (3) REDACTED alleged conduct injured the other party, Amneal.

259. Amneal cannot prove that REDACTED allegedly acted in bad faith REDACTED REDACTED

260. Amneal does not have any factual basis for its allegations of bad faith conduct by REDACTED

261. Amneal cannot show that the alleged breach concerned information that was not already in the public domain.

262. Amneal cannot show that REDACTED

1. There Is No Basis for Amneal's Allegation that REDACTED Acted in Bad Faith

263. Amneal cannot prove by clear and convincing evidence that REDACTED was involved in alleged fraud or deceit or acted unconscionably or in bad faith REDACTED

[4] Plaintiffs note that Amneal's pleadings do not allege any REDACTED in this case, and accordingly, Plaintiffs reserve the right to respond fully to any such allegations should they be made.

REDACTED which later issued as the Chang '740 patent.

264. Amneal does not have any factual basis for its allegation that REDACTED allegedly conveyed any of Amneal's confidential information REDACTED REDACor used any of Amneal's confidential information to engage in the prosecution of the Chang '676 application.

265. On June 6, 2008, patentees filed the Chang '676 application with the PTO. *See* PTX 2.

266. On September 27, 2011, after the filing of the Chang '676 application, Amneal made a deliberate decision to send a Paragraph IV Notice Letter regarding the Chang '532 patent ("Chang '532 patent Notice Letter") to the legal department of Galderma, setting forth Amneal's allegations that its Generic Product does not infringe the claims of the Chang '532 patent or that the claims of the Chang '532 patent are invalid. *See* PTX 10.

267. Amneal's Chang '532 patent Notice Letter is a public document and is not confidential.

268. Amneal's Chang '532 patent Notice Letter states "AMNEAL'S ANDA product does not contain a DR portion that is in the form of pellets. Therefore, the manufacture, use, importation, sale or offer for sale of AMNEAL'S ANDA product would not literally infringe any claim of the Chang '532 patent." *See* PTX 10, at p. 8.

269. On August 12, 2011, prior to Plaintiffs' receipt of Amneal's Chang '532 patent Notice Letter, the patentee for the Chang '676 application filed an Amendment in response to a March 23, 2011 Office Action with the PTO ("August 12, 2011 Amendment"). As of that

Amendment, several of the claims (*e.g.*, independent claim 49) did not contain any limitation to a DR portion in the form of pellets. *See* PTX 6, at GLD0280209-11.

270. REDACTED did not convey any Amneal confidential information, including information derived from Amneal's ANDA, orally or in writing, to Plaintiffs' patent prosecution counsel at any time. *See* PTX 296, at ¶ 3.

271. REDACTED never used any Amneal confidential information, including information derived from Amneal's ANDA, to engage, formally or informally, in patent prosecution for Plaintiffs. *See* PTX 296, at ¶ 3.

2. There Is No Injury To Amneal

272. Amneal cannot prove by clear and convincing evidence that the alleged conduct of REDACTED resulted in injury to Amneal.

273. Amneal cannot prove by clear and convincing evidence that REDACTED alleged conduct had an immediate and necessary relationship to the equity sought by Plaintiffs in this litigation.

274. The information contained in Amneal's Chang '532 patent Notice Letter was not confidential and was publicly available.

275. As a result of Amneal's public, nonconfidential disclosures in its Chang '532 patent Notice Letter, Amneal's allegations that its Generic Product does not contain a "DR portion that is in the form of pellets" and thus allegedly does not infringe the claims of the Chang '532 patent were a matter of public record as of September 27, 2011, prior to any agreement to enter into Amneal's OCA or any production by Amneal of confidential information regarding its Generic Product.

276. **[*Plaintiffs reserve the right to supplement their Issues of Fact to be Litigated at Trial with respect to Defendants' allegations regarding unclean hands, for which discovery requested by Defendants is presently ongoing.*]**

E. Enforceability Of The Chang '740 Patent In Light Of Amneal's Breach Of Contract Allegations

277. Amneal cannot show that any of the asserted claims of the Chang '740 patents are unenforceable on the grounds of breach of contract.

278. Amneal cannot prove the elements required for an action for breach of contract, including whether there is (1) a contract; (2) performance of the contract by one party; (3) breach of the contract by the other; and (4) damages caused by the alleged breach of contract.

279. Amneal cannot prove that it suffered any damages as a result of REDACTED alleged breach of Amneal's OCA.

280. Amneal cannot prove that but for the alleged misconduct, Amneal would be in a different position regarding Amneal's infringement of the Chang '740 patent.

281. Amneal cannot prove that the alleged conduct of REDACTED directly and proximately caused Amneal any damage.

282. Amneal cannot show that the alleged breach of Amneal's OCA concerned information that was not already in the public domain prior to the time of the alleged breach.

283. REDACTED did not convey any Amneal confidential information, including information derived from Amneal's ANDA, orally or in writing, to Plaintiffs' patent prosecution counsel at any time. *See* PTX 296, at ¶ 3.

284. REDACTED never used any Amneal confidential information, including information derived from Amneal's ANDA, to engage, formally or informally, in patent prosecution for Plaintiffs. *See* PTX 296, at ¶ 3.

285. **[*Plaintiffs reserve the right to supplement their Issues of Fact to be Litigated at Trial with respect to Defendants' allegations regarding breach of contract, for which discovery requested by Defendants is presently ongoing.*]**

V. CONCLUSION

286. Amneal infringes the asserted claims of the Chang patents.

287. Amneal cannot prove by clear and convincing evidence that the asserted claims of the Chang patents are invalid or unenforceable.

EXHIBIT 3

EXHIBIT 3

AMNEAL'S STATEMENT OF CONTESTED FACTS

TABLE OF CONTENTS

Pursuant to Local Rule 16.3(c)(4), Defendants Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals Co. (I) PVT. Ltd. ("Amneal") submit the following issues of fact that remain to be litigated. The following statements are not exhaustive, and Amneal reserves the right to prove any matters identified in its pleadings, interrogatory responses, and/or expert reports. Amneal also intends to offer evidence as to the issues of fact and issues of law identified in this pretrial order. Amneal further intends to offer evidence to rebut evidence offered by Plaintiffs.

To the extent that Amneal's statement of the issues of law that remain to be litigated, which is submitted as Exhibit 5, contain issues of fact, those issues are incorporated herein by reference. Moreover, if any issue of fact identified below should properly be considered an issue of law, then such statement shall be considered to be part of Amneal's statement of issues of law that remain to be litigated. Amneal incorporates by reference its expert reports in support of any proof to be presented by expert testimony.

I. BACKGROUND ON THE CHANG PATENTS

1. U.S. Patent Nos. 7,749,532 ("the '532 patent") and 8,206,740 ("the '740 patent") (together "patents-in-suit"), both entitled "Once-Daily Formulations of Tetracyclines," relates to controlled release doxycycline formulations, wherein the composition when administered once-daily "give[s] steady state blood levels of doxycycline of a minimum of 0.1 µg/mL and a maximum of 1.0 µg/mL."

2. The patents-in-suit are directed to once-daily oral pharmaceutical compositions containing doxycycline, a method of treating rosacea with an oral pharmaceutical composition containing doxycycline, and a process for preparing the pharmaceutical composition.

3. The patents-in-suit are "concerned with once-daily compositions of tetracyclines, which can be used for the treatment of acute or chronic diseases, for instance those with inflammatory components." '740 patent, col. 1:6-9.

4. The patents-in-suit describe generally oral pharmaceutical compositions containing tetracyclines such as doxycycline for the treatment of collagenase destructive enzyme-dependent diseases, such as periodontal disease and acne, and acute and chronic inflammatory disease states, such as rosacea and arthritis.

II. AMNEAL DOES NOT INFRINGE ANY OF THE ASSERTED PATENT CLAIMS

5. Plaintiffs cannot meet their burden of proving that Amneal has infringed, either literally or under the doctrine of equivalents, any asserted claims of the ’532 and ’740 patents.

6. Plaintiffs cannot meet their burden of proving that Amneal will infringe, either literally or under the doctrine of equivalents, any asserted claims of the ’532 and ’740 patents if it makes, uses, offers to sell, sells or imports its proposed ANDA product prior to the expiration of the ‘532 and ’740 patents.

7. Plaintiffs cannot meet their burden of proving that Amneal will induce physicians, other healthcare professionals, caregivers or patients to infringe any of the asserted claims of the ’532 and ’740 patents.

8. Plaintiffs cannot meet their burden of proving that Amneal will contribute to the infringement of any of the asserted claims of the ’532 and ’740 patents.

III. THE ASSERTED PATENT CLAIMS ARE INVALID

9. Each asserted claim of the patents-in-suit is invalid as anticipated and/or obvious in view of the Ashley references, their commercial embodiment (the prior art Periostat® tablets), the ’748 patent, and the CollaGenex Pharmaceuticals 2001 Annual Report, either alone or in combination as described below.

A. Prior Art to the Chang Patents

1. The Level of Ordinary Skill In The Art

10. A person of ordinary skill in the art as of the effective filing date of the patents-in-suit would have a Ph.D. in a field related to pharmaceutical formulation and have experience with modified-release solid oral dosage forms with a few years of practical experience in the field.

11. In addition, with regards to the pharmacokinetic-specific subject matter claimed in the patents-in-suit, a person of ordinary skill in the art would also have an understanding of statistical formulas and principles necessary to evaluate pharmacokinetic parameters as it relates to drug development.

12. A person of ordinary skill would work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team, to solve a given problem.

2. The Scope and Content Of The Prior Art

(a) Periostat® (1998)

13. CollaGenex's Periostat® product was approved by the FDA on September 30, 1998, pursuant to New Drug Application No. 50-744.

14. Periostat®'s approval date is before the date of invention claimed in the Chang patents.

15. Periostat® is prior art under 35 U.S.C. 102(a) and 102(b) because it was publicly known, used, and sold in the United States before the earliest priority date for the patents-in-suit.

16. In connection with its approval, the FDA prepared an Approval Package that contains information concerning Periostat® that the FDA makes available to the public ("Periostat® Approval Package").

17. Periostat® was approved from an application that was approved after July 1, 1975.

18. For any applications approved after July 1, 1975, the FDA makes its corresponding Approval Package immediately available for public disclosure. 21 C.F.R. § 314.430.

19. The Periostat® Approval Package was publicly available immediately following Periostat®'s approval by the FDA.

20. An Approval Package, like the one for Periostat®, is a publicly-available document that may be obtained from the FDA through a Freedom of Information Act request or through accessing the FDA website. *See* Clark Dep. At 20-22 and Exhibit 3.

21. Within the Periostat® Approval Package is a section entitled "Clinical Pharmacology and Biopharmaceutics Review(s)," which discloses data concerning pharmacokinetic studies performed with 20 mg, 40 mg, and 50 mg doses of doxycycline hyclate.

22. The Clinical Pharmacology and Biopharmaceutics Review(s) discloses two steady-state studies involving low doses of doxycycline: (1) Study No. C1-95-102; and (2) Study 92-034.

23. Study No. C1-95-102 involved an open-label, multi-dose, three-treatment crossover study of steady-state pharmacokinetic behavior, which showed that a single 20 mg dose of doxycycline administered once-daily would achieve steady-state blood levels above 0.1 μg/ml and below 1.0 μg/ml.

24. Study No. 92-034 involved a multi-dose, three-treatment crossover study of steady-state pharmacokinetic behavior, which sought to "determine at the steady-state for each

treatment regimen whether mean C_{max} exceeded 1.0 mcg/ml, which is believed to be the lowest serum concentration exerting a systemic antimicrobial effect."

25. Study No. 92-034 concluded that both Treatment A (20 mg administered twice daily) and Treatment B (40 mg administered once daily) achieved steady-state blood levels below the 1.0 μg/ml threshold level.

26. The results of Study 92-034 also indicated that absorption of doxycycline is nearly dose linear at low doses, reporting that "[a]fter normalized for dose, the absorption from 20 mg doxycycline capsule twice daily was similar to that from 50 mg Vibramyacin® [doxycycline] based on both AUC (0-24) and C_{max} values."

27. Oracea® is a result of CollaGenex's efforts to develop a once-daily Periostat® formulation.

(b) U.S. Provisional Application No. 60/281,854

28. On April 5, 2001, CollaGenex filed U.S. Provisional Patent Application No. 60/281,854 ("the '854 application"), titled "Controlled Delivery of Tetracycline and Tetracycline Derivatives," naming Robert Ashley as the sole inventor.

29. The '854 application discloses controlled-release compositions for delivering tetracycline compounds, including doxycycline. The '854 app. at 5:8 – 6:24.

30. The '854 application explains that doxycycline compounds "have a number of therapeutic uses in addition to their anti-microbial properties." *Id.*, 2:22-4:23.

31. Some of these non-anti-microbial therapeutic uses include the treatment of acne and other skin diseases. *Id.*, 4:10-17.

32. The '854 application is directed to "the need for a composition for controlled delivery of tetracycline to a host that, unlike conventional compositions, provides a dosage

below that which is required for an anti-microbial response in the host at a relatively constant serum level with a longer serum half-life." *Id.*, 5:1-4.

33. The '854 application explains that the disclosed compositions allow for once-daily dosing. *Id.*, 6:26-29.

34. The '854 application discloses the target therapeutic window to be achieved by once-daily dosing, the benefits of such a dosing regimen, and compositions for achieving that therapeutic window.

35. The '854 application describes the target therapeutic window in terms of blood serum concentrations.

36. The '854 application explains that the target blood levels should be "between about 0.1 and 1.0 μg/ml, preferably between about 0.3 and 0.8 μg/ml." *Id.* at 5:15-19.

37. The '854 application states for doxycycline specifically, "the preferred blood serum level … is 0.4 – 0.8 μg/ml. over a period of 12-24 hours." *Id.*, 5:21-22.

38. The '854 application indicates that "[t]his release profile should be maintained at a substantially constant rate for between about 6-24 hours." *Id.*, 5:18-19.

39. The '854 application discloses that the dosage form should maintain blood levels between 0.4 and 0.8 μg/ml for between 6 to 24 hours.

40. The '854 application identifies several benefits associated with once-daily dosing of low doses of tetracycline compounds, including avoiding undesirable side effects, improved patient compliance by once or twice daily dosing, avoidance of a potential food effect, and a reduced risk of the phototoxicity typically associated with tetracycline compositions. *See id.* at 6:21 – 7:12.

41. The ‘854 application also describes several different formulation approaches that will achieve the target blood levels.

42. The ‘854 application explains that the composition can be “in the form of a liquid as a suspension or solution, or alternatively in solid form, such as a tablet, particle, capsule or soft gel.” *Id.*, 12:12-14.

43. The ’854 application further specifies that the “the form can be polymeric capsules filled with solid particles which can, in turn, be made to release tetracycline according to a known pattern or profile.” *Id.*, 12:14-16.

44. The ‘854 application further states, “[s]uch particles can also be made to have more than one release profile so that over an extended time the combined release patterns provide a pre-selected profile.” *Id.*, 12:16-18.

45. The ‘854 application further explains that different controlled-release agents can be used to achieve the desired release profile, which include “an instantaneous-release agent, a delayed-release agent, a sustained-release agent, or any combination thereof.” *Id.* at 10:18-20.

46. The ’854 application explains that “[a]n instantaneous release agent is self-explanatory in that it refers to an ingredient which promotes or enhances immediate release to the host.” *Id.* at 10:22-26.

47. The ’854 application also explains that “[a] delayed release agent is an ingredient which prevents the active ingredient, *i.e.*, tetracycline, from being made available to the host until sometime after initial administration.” *Id.* at 11: 4-6.

48. The ‘854 application states “delayed release agent prevents release of tetracycline until some time in the future.” *Id.* at 11:6-7.

49. The ‘854 application also states “[e]xamples of delayed release agents include, but are not limited to, polymeric or biodegradable coatings or matrices, including cellulose polymers, and combinations thereof.” *Id.* at 11:8-10.

50. Because of the small number of possible combinations of these three agents disclosed in the ’854 application—“an instantaneous-release agent, a delayed-release agent, a sustained-release agent, or any combination thereof”—each of the possible combinations are disclosed.

51. Thus, the ’854 application discloses necessarily a combination of IR and DR agents. Further, this is also necessarily a disclosure of all ratios of IR to DR agents that will achieve serum concentrations between 0.1 μg/ml. and 1.0 μg/ml., more preferably between 0.4 μg/ml. and 0.8 μg/ml. for doxycycline.

52. In the passage below, *inter alia*, the ‘854 application provides guidance as to what portion of the drug should be released immediately and, consequently what portion of the drug may be delayed:

> In a preferred embodiment, the controlled-release composition is entrapped in the upper portion of the gastrointestinal tract, for example, the stomach or duodenum…. It is preferred that at least 50%, more preferably 80% of the tetracycline in the composition be release in the upper GI tract.

Id., 16:9-14.

53. A skilled artisan would understand this disclosure in the ‘854 application to teach that it is preferable to release 50-80% of the doxycycline in the upper GI tract (*i.e.*, the stomach or duodenum).

54. This teaching in the ‘854 application is consistent with the knowledge in the art at the time that doxycycline is best absorbed from the duodenum.

55. Because the '854 application teaches that it is preferred that at least 50%, more preferably greater than 80% of the doxycycline be released in the upper GI tract, the '854 application at p. 16:9-14, one of ordinary skill in the art would immediately envisage a composition comprising, *e.g.*, at least 50%, more preferably, greater than 80% doxycycline in an IR form and the remainder in a DR form.

(c) WO02/083106 and U.S. Patent Application 10/474,240

56. On April 5, 2002, CollaGenex filed U.S. Patent Application No. PCT/US2002/10748, which published as WO 02/083106 on October 24, 2002 ("the '106 application").

57. The '106 application claims priority to the '854 application and identifies Robert A. Ashley as the sole inventor.

58. The U.S. national stage of the '106 application is U.S. Patent Application No. 10/474,240 ("the '240 application").

59. The '106 application qualifies as prior art under 35 U.S.C. 102(a) because it has a publication date before the invention claimed in the Chang Patents.

60. Because the '240 application is the corresponding national stage of the '106 application, their disclosures are identical.

61. Galderma's patent counsel prosecuted the '240 application.

62. The '106 application discloses controlled-release compositions for delivering tetracycline compounds, including doxycycline. The '106 app., at 1:17-20.

63. The '106 application discloses that doxycycline compounds "have a number of therapeutic uses in addition to their anti-microbial properties." *Id.*, 1:34 - 4:6.

64. Some of the non-anti-microbial therapeutic uses disclosed in the '106 application include the treatment of acne and other skin diseases. *Id.*, 3:1-24.

65. The ’106 application is directed to “the need for a composition for improved delivery of tetracycline compounds to a mammal that, unlike conventional compositions, provides a dosage below that which is required for an antibiotic response in the mammal at a relatively constant serum level with a longer serum half-life,” *Id.*, 4:8-12, which allows for once-daily dosing. *Id.*, 6:7-9.

66. The ’106 application explains that the desired blood serum concentration levels are “between about 0.1 and 1.0 μg/ml, preferably between about 0.3 and 0.8 μg/ml.” *Id.*, 4:23-26.

67. For doxycycline specifically, the ’106 patent explains that “the preferred blood serum level … is 0.4 – 0.8 μg/ml over a period of 12-24 hours.” *Id.*, 4:29-30.

68. The ’106 application indicates that “[t]his release profile should be maintained at a substantially constant rate for between about 6-24 hours.” *Id.*, 4:26-27.

69. Thus, the ’106 application also discloses that the dosage form should maintain blood levels between 0.4 and 0.8 μg/ml for between 12 to 24 hours for doxycycline.

70. The ’106 application identifies several benefits associated with once-daily dosing of low doses of tetracycline compounds, *see id.* at 6:1-24, including avoiding undesirable side effects, improved patient compliance by once or twice daily dosing, avoiding of potential food effects, and a reduced risk of phototoxicity associated with tetracycline compounds.

71. The ’106 application also describes several different formulation approaches that will achieve the target blood levels, explaining that the composition can be “in the form of a liquid as a suspension or solution, or alternatively in solid form, such as a tablet, pellet, particle, capsule, or soft gel.” *Id.*, 11:25-28.

72. The ’106 application further specifies that the dosage form “can be polymeric capsules filled with solid particles which can, in turn, by made to release the tetracycline compound according to a known pattern or profile.” *Id.,* 11:27-29.

73. The ’106 application further explains that “[s]uch particles can also be made to have more than one release profile so that over an extended time the combined release patterns provide a pre-selected profile.” *Id.,* 11:29-31.

74. The ’106 application also indicates that “[o]ne embodiment of the unit dosage form is a capsule which contains beadlets,” *Id.,* 15:20, explaining that “[w]ithin each capsule are beadlets which are coated with various coatings that dissolve at different pH levels.” *Id.,* 15:21-22.

75. The ’106 application further explains that different controlled-release agents can be used to achieve the desired release profile, which include “an instantaneous-release agent, a sustained-release agent, a delayed-release agent, or any combination thereof.” *Id.,* 9:30 – 10:2.

76. The ’106 application explains that “[a]n instantaneous release agent refers to an ingredient which promotes or enhances immediate release to the mammal.” *Id.,* p. 10:4-5.

77. The ’106 application also explains that “[a] delayed release agent is an ingredient which prevents the tetracycline compound from being made available to the host until some time after initial administration.” *Id.,* 10:17-19.

78. The ’106 application explains “delayed release agent prevents release of tetracycline until some time in the future,” *Id.* at 10: 19-20, and disclosing that “[e]xamples of delayed release agents include, but are not limited to, polymeric or biodegradable coatings or matrices, including cellulose polymers, and combinations thereof.” *Id.,* 10:20-22.

79. The '106 application references twelve other patents as providing examples of controlled-release agents for use with the invention. *Id.*, col. 9:1-5. For example, the referenced U.S. Patent No. 4,837,030 discloses several suitable controlled-release agents that a skilled artisan would also understand to be useful as delayed release agents, including: hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose succinate, polymers and copolymers of (meth)acrylic acid and (meth)acrylic acid methyl ester. *See* U.S. Patent No. 4,837,030, col. 6:42-64.***

80. The '106 application's disclosure of a "capsule [with] beadlets which are coated with various coatings that dissolve at different pH levels," *id.*, 15:21-22, discloses to one of ordinary skill in the art that the dosage form should have a ratio of different beadlets to achieve the desired therapeutic serum concentration levels.

81. When read in light of the '106 application's disclosure of using combinations of IR and other CR agents to achieve the desired therapeutic serum concentrations, a skilled artisan would understand this to mean that one composition disclosed by the '106 application is a capsule containing IR and DR beadlets that are combined in a ratio to achieve the desired therapeutic serum concentrations.

82. The '106 application teaches that the "amount of doxycycline" can be determined by one skilled in the art." *Id.*, 13:14-16.

83. In the passage below, the '106 application provides guidance as to what portion of the drug should be released immediately and, consequently what portion of the drug may be delayed:

> In a preferred embodiment, the controlled-release composition is entrapped in the upper portion of the gastrointestinal tract, for example, the stomach or duodenum…. It is preferred that at least 50%, more preferably 80% of the tetracycline in the composition be release in the upper GI tract.

Id., 16:9-14.

84. A skilled artisan would understand this disclosure to teach that it is preferable to release 50-80% of the doxycycline in the upper GI tract (*i.e.* the stomach or duodenum), which is consistent with the knowledge in the art at the time that doxycycline is best absorbed from the duodenum.

85. The ’106 application discloses a once-daily pharmaceutical composition of doxycycline that comprises immediate release and delayed release beadlets, at least one pharmaceutically acceptable excipient, and that provides blood levels between 0.4 and 0.8 μg/ml.

86. On December 22, 2010, Galderma's patent counsel amended the claims of the '240 application and, inter alia, sought allowance of application claim 82.

87. On April 4, 2011, the PTO allowed claim 82, as amended, of the '240 application.

88. On July 5, 2011, Galderma paid the issue fee in connection with claim 82 of the '240 application.

89. Galderma presented, prosecuted, and obtained allowance of the following claim:

> 82. A controlled release pharmaceutical capsule consisting of beadlets, wherein the beadlets consist of:
>
> a. doxycycline,
>
> b. a controlled release agent, wherein the controlled release agent is either:
>
> 1. an instantaneous-release agent or
>
> 2. a polymeric and/or biodegradable delayed-release agent, and
>
> c. at least one pharmaceutical excipient other than a controlled release agent,
>
> wherein the capsule consists of beadlets having the instantaneous-release agent and beadlets having the delayed release agent,

> wherein the doxycycline is physically associated with the controlled-release agents to provide a release-profile in a human upon administration whereby the human is treated with doxycycline at a dose substantially without antibiotic activity, and
>
> wherein the dose provides a serum level of about 0.4 to 0.8 µg/ml over a period of 12 to 24 hours.

(December 22, 2010 Amendment in Response to September 9, 2010, Final Office Action and Substance of Interview); Clark Dep. at 154-173.

90. By presenting and obtaining allowance of this claim, Galderma represented to the PTO and to the public generally that the ’240 application (and, therefore, the ’106 application) had support in the written description. *Id.* at AMORA_00132171.

91. By having the ’106 and ’240 application claim priority to the ’854 applications, Galderma has represented to the PTO and the public generally that the ’854 application provides support in the written description for claim 82.

92. The PTO Examiner initially rejected claim 82 on the basis that it does not recite in terms of milligrams how much doxycycline should be provided in the immediate and delayed-release portions.

93. To overcome this objection, Galderma submitted the declaration of Dr. Robert O. Williams (“Williams Decl.”), a tenured professor at the University of Texas, College of Pharmacy.

94. Dr. Williams’s declaration explained that “a serum level provides a more accurate description of a doxycycline dose than does the amount of doxycycline placed into a capsule.” Williams Decl., ¶ 3.

95. Dr. Williams further explained that based on what was known in the art about doxycycline and the ’240 application’s disclosure, “a skilled artisan would be able to readily

deduce what administered dose of doxycycline would provide a serum level of about 0.4 to 0.8 μg/ml doxycycline." *Id*, ¶ 4.

96. Galderma also represented to the PTO that Claim 82 does not have a "sustained release agent."

97. Galderma repeated this assertion again, stating that "**Claim 82 cannot include a prolonged release agent.**"

(d) U.S. Patent No. 7,232,572 and W0 02/080932

98. On April 5, 2002, CollaGenex filed U.S. Patent Application No. 10/117,709, which ultimately matured into U.S. Patent No. 7,232,572 ("the '572 patent").

99. The '572 patent is entitled "Methods of Treating Rosacea," and identifies Robert A. Ashley as the sole inventor.

100. Although the '572 patent did not issue until June 19, 2007, it claims priority to U.S. Provisional Application No. 60/281,916, dated April 5, 2001, and U.S Provisional Patent Application No. 60/325,489, dated September 26, 2001.

101. Accordingly, the '572 patent is prior art under 35 U.S.C. § 102(e)(2), because it was granted on an application filed before the invention of subject matter claimed by the patents-in-suit.

102. Each of the allowed claims of the '572 patent is supported by an enabling disclosure in the '572 patent specification.

103. CollaGenex filed U.S. Patent Application No. PCT/US2002/0747, on April 5, 2002, and it published on October 17, 2002, as WO 02/080932 ("the '932 application").

104. The '932 application is titled "Methods of Treating Acne" and identifies Robert A. Ashley as the sole inventor.

105. The ’932 application qualifies as prior art under 35 U.S.C. § 102(a) because it published prior to the date of invention of the Chang Patents.

106. The ’572 patent and the ’932 application claim the benefit of the same priority applications and have nearly identical specifications, the only difference between their respective specifications being that the ’572 patent contains an additional disclosure regarding the treatment of telangiectasia, s*ee* ’572 patent, col. 4:46-67, which is not relevant to issues in this case.

107. Galderma owns both the ’572 patent and the ’932 application through an assignment by CollaGenex.

108. The ’572 patent is directed to the treatment of various acne conditions, including “[a]cne rosacea.” ’572 patent at col. 4:25-45.

109. The ’572 patent discloses the use of tetracyclines administered at low doses to treat these conditions, *see id.* at col. 5:20-61, and specifically discloses doxycycline. *Id.* at col. 5:20-25.

110. The ’572 patent explains the desired therapeutic window in terms of achieving drug serum concentration that are “10-80% of the minimum antibiotic serum concentration” for the administered tetracycline.” *Id.* col., 6:34-39.

111. For doxycycline, the threshold antibiotic level “based on steady-state pharmacokinetics” is 1.0 µg/ml. *See id.* col. 6:59-62 (stating “[s]ome examples of the plasma antibiotic threshold levels of tetracyclines based on steady-state pharmacokinetics are as follows: 1.0 µg/ml for doxycycline; 0.8 µg/ml for minocycline; and 0.5 µg/ml for tetracycline”).

112. The ’572 patent explains that the therapeutic window for doxycycline corresponds to steady-state serum concentration levels “between about 0.1 and 0.8 µg/ml, more preferably between 0.4 and 0.7 µg/ml.” *Id.* col. 6:55-58.

113. Alternatively, the '572 patent discloses that the administered amount of drug can also be described by the daily dosage amount, *Id.*, col. 5:62-64, explaining that "[t]wo ways in which to describe the administered amount of a tetracycline compound is by daily dose, and by serum concentration."

114. For doxycycline, this corresponds to the daily administration of 40 mg of doxycycline, *Id.*, col. 6:9-13, because according to the '572 patent "[e]xamples of the maximum non-antibiotic doses of tetracyclines based on steady-state pharmacokinetics are as follows: 20 mg/twice a day for doxycycline."

115. The '572 patent discloses once-daily administration of the disclosed compounds. *Id.*, col. 9:25-27.

116. The '572 patent discloses Periostat® as an "especially preferred embodiment." *Id.*, col. 6:19-23.

117. According to its approved prescribing information as of February 2, 2001, Periostat® Tablets contained 23 mg of doxycycline hyclate (equivalent to 20 mg of doxycycline), and the following inert ingredients: hydroxpropylmethlcellulose, lactose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin. *See* http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/ 50783LBL.pdf.

118. Although the '572 patent discloses the immediate release Periostat® tablet product as one embodiment, it also discloses that "tetracycline compounds may be administered by sustained release." *Id.*, col. 9:28-29.

119. According to the '572 patent, "sustained release" refers to "a method of drug delivery to achieve a certain level of the drug over a particular period of time." *Id.*, col. 9:29-31.

120. The ’572 patent discloses compositions for achieving the desired therapeutic window and the benefits of once-daily dosing through its incorporation by reference of the ‘854 application described above.

121. The ’572 patent points to the ‘854 application for the express purposes of providing a “[f]urther description of methods of delivering tetracycline compounds by sustained release.” *Id.*, col. 9:32-34.

122. The disclosures of the ‘854 application also apply to the ’572 patent’s disclosure.

123. The ’572 patent claims methods of administering 40 mg of doxycycline by sustained release (claim 10, which depends from claims 1, 4, 5, 6, 7, and 9) to achieve serum concentrations between 0.1 to about 0.8 μg/ml. *Id.*, 32:22-67.

124. It also claims a method of administering 40 mg of doxycycline once-daily (claim 26, which depends from claims 20 and 23), which is presumed to be enabled by the specification. *Id.*, 34:1-27.

(e) U.S. Patent No. 5,348,748

125. U.S. Patent No. 5,348,748, issued September 20, 1994 (“the ’748 patent”), and is titled “Pulsatile Once-a-Day Delivery Systems for Minocycline.”

126. The ’748 patent is prior art under 35 U.S.C. §102(b) as it published more than one year before the effective filing date of the patents-in-suit.

127. The ’748 patent is directed to once-daily delivery systems for minocycline, which is a second-generation tetracycline that has similar properties to doxycycline.

128. The ‘854 application, the ’106 application, the ’240 application, the ’932 application, and the ’572 patent all identify both minocycline and doxycycline as tetracyclines suitable for use in low dose tetracycline treatments.

129. Both doxycycline and minocycline have long half-lives and similar known absorption windows.

130. A prior art once-daily minocycline formulation is a reference that a skilled artisan would have considered when formulating a once-daily doxycycline treatment.

131. The '748 patent explains that its object is "a once-a-day delivery system which maintains therapeutic blood level concentrations of the medicament in a patient for twenty-four hours." '748 patent, col. 1:12-15.

132. The '748 patent also discloses formulations that include a pulsed-release formulation comprised of a major portion of a first pulse of quick release granules and a minor portion of a second pulse of coated granules. *Id.*, col. 1:17-22.

133. It also discloses that improved bioavailability can be achieved by "increasing the ratio of quick release initial loading pellets to slow release secondary loading coated pellets and by using a modified coating composition for the latter." *Id.*, col. 3: 48-52.

134. The "secondary loading pellets" disclosed in the '732 patent are coated with a pH-sensitive coating, *id.*, col. 3:55-58—*i.e.* an enteric polymer.

135. The '748 patent explains that minocycline has greater absorption in the upper gastrointestinal tract (stomach and duodenum) and reduced absorption in the lower portions of the gastrointestinal tract. *Id.*, col. 2:19-27.

136. Thus, the '748 patent discloses that "use of a higher level of quick release granules in proportion to delayed release granules is believed to result in a higher absorption of minocycline because minocycline is preferably absorbed in the duodenum and jejunum." *Id.*, col. 7:21-25.

137. The ’748 patent discloses that its formulation can be used to deliver dosage amounts ranging from 25 mg to about 400 mg of minocycline. *Id.*, col. 8:11-16.

138. The ’748 patent, therefore, discloses formulations that achieve blood levels that may be in the doxycycline non-antibiotic range taught by the prior art. *See, e.g.,* “748 patent, col 1: 53-55.

139. The ’748 patent also discloses a range of ratios of quick release to coated granules, ranging from 51:49 to 80:20. ’748 patent, col. 8:16-24; *see also* col. 5:11-21.

140. The ’748 patent teaches that its disclosed formulations have “superior controlled and prolonged delivery” of the active ingredient, “sustain a desired blood level concentration in a subject for a relatively long period of time of up to twenty-four hours,” and allow for “fewer and lessened side effects, including reduced gastroirritability, and better subject compliance.” *Id.,* col. 6:35-69.

141. The ’748 patent further provides illustrative examples of formulations within the scope of its disclosure. *Id.*, col. 13:45 - col. 16:52.

142. A number of suitable coatings, including enteric coatings are disclosed in the ’748 patent, as well as other excipients. *Id.* col. 8:65 - col. 9:24, col. 10:8-22, col. 11:66 – 12:8.

(f) The CollaGenex Pharmaceuticals 2001 Annual Report

143. The CollaGenex Pharmaceuticals 2001 Annual Report (“the 2001 Annual Report”) is prior art under 35 U.S.C. § 102(b) because it was published more than one year prior to the effective filing date of the patents-in-suit.

144. The 2001 Annual Report discloses that Periostat® showed efficacy in treating inflammatory acne in adults. he 2001 Annual Report at 8.

145. The 2001 Annual Report also discloses that CollaGenex contracted for an initial feasibility study and formulation development work for a once-a-day formulation of Periostat®. The 2001 Annual Report at 12.

B. The Asserted Claims of the Patents-in-Suit are Invalid in View of the '572 Patent or, in the Alternative, the '932 Application

1. The '572 Patent or the '932 Application Anticipates Each Asserted Claim of the Patents-in-Suit.

146. Each limitation of claims 1, 2, 5-15, and 19-22 of the '740 patent and claims 1-8 and 15-21 of the '532 patent are disclosed as arranged in the claims, expressly and/or inherently, by the '572 patent.

147. Each limitation of claims 1, 2, 5-15, and 19-22 of the '740 patent and claims 1-8 and 15-21 of the '532 patent are also disclosed as arranged in the claims, expressly and/or inherently, by the '932 application.

148. The written descriptions contained in the '572 patent and the '932 application are identical in all material respects, so reference to the '572 patent and the '932 application are made together for ease reference, not as a combination of separate references.

(a) Claim 1 of the '532 Patent and Claim 1 of the '740 Patent

149. Claim 1 of the '532 patent and claim 1 of the '740 patent share the following three limitations:

(i) An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml,

150. The '572 patent and the '932 application expressly disclose oral pharmaceutical compositions of doxycycline that will give steady state blood levels of a minimum of 0.1 µg/ml. and a maximum of 1.0 µg/ml.

151. The ’572 patent is directed to the administration, including oral administration, of pharmaceutical compositions. ’572 patent, col. 8:52-56.

152. The ’572 patent discloses and claims the oral administration of doxycycline compositions to achieve drug serum concentrations between 0.1 to 0.8 μg/ml. *Id.*, col. 6:55-58; col. 32:55-58.

153. The serum concentrations recited by the ’572 patent are based on steady-state pharmacokinetics. *Id.*, col. 6:59-62.

154. The ’932 application contains the same disclosures. *See, e.g.*, ’932 app., 14:14-17 (oral administration of a pharmaceutical composition); 10:25-29 (doxycycline blood levels between 0.1 and 0.8 μg/ml); 55:8-10 (same); 11:1-3 (use of steady-state pharmacokinetic levels).

155. The ’572 patent directs that the disclosed “tetracycline compounds can be administered orally by any method known in the art”, including “tablets, capsules, [and] pills.” ’572 patent, col. 8:51-56.

156. The ’572 patent expressly discloses and claims once-daily administration. *See e.g.*, *id.*, col. 9:26-27; claims 10 and 26. The ’932 application contains the same disclosures. *See, e.g.*, ’932 app., 14:14-17 (disclosing suitable dosage forms); 15:19-21 (administration once per day); 55:18-19 (administration of 40 mg).

(ii) the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline (claim 1 of the ’740 patent)/ (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with at least one enteric polymer (claim 1 of the ’532 patent);

157. The ’572 patent and the ’932 application disclose compositions comprising an IR portion comprising 30 mg of doxycycline and a DR portion comprising 10 mg of doxycycline.

158. The ’572 patent discloses and claims the once-daily administration of 40 mg of doxycycline by sustained release. *See e.g., id.,* col. 9:26-41; claims 10 and 26.

159. The ’572 patent also discloses and claims administering compositions by sustained release, which it defines to be delivering drug “to achieve a certain level of drug over a particular time period.” *Id.,* col. 9:28-41. The ’932 application contains the same disclosures. *See e.g.,* 932 app., 15:19 – 16:2.

160. The formulations for achieving this sustained release are set forth in the ‘854 application, which is expressly incorporated by reference in its entirety by the ’572 patent and the ’932 application. *See* ’572 patent, col. 9:33-37; ’932 app., 15:26-30.

161. The ‘854 application describes various approaches for formulating controlled release compositions, but one such approach is through the use of IR and DR agents (*i.e.* IR and DR portions). *See* ‘854 app., 10:18-20 and 11:4-9.

162. It further specifies that one dosage form that may be employed is a capsule with particles that have different release profiles so as to achieve a target profile. *Id.,* 12:12-18.

163. The ’572 patent and the ’932 application teach that 40 mg of doxycycline should be administered once-daily by sustained release and that one approach for achieving that sustained release is through the use of IR and DR components.

164. Because the ’572 patent and the ’932 application disclose the once-daily administration of 40 mg of doxycycline using IR and DR components, it necessarily discloses the full range of IR and DR ratios—from 40:0 (IR:DR) to 0:40 (IR:DR).

165. Although there may be 40 theoretical IR:DR ratio combination disclosed in this range, assuming 1 mg units, as a practical matter there are far fewer ratios that a skilled artisan would be motivated to select.

166. A formulator would want to ensure that the dosage form is reproducible on the commercial scale and, therefore, would take into consideration manufacturing and process considerations.

167. The ’572 patent and the ’932 application expressly discloses the 30:10 (IR:DR) ratio even though it does not use those precise terms.

168. The patents-in-suit state that at least thirty-percent of the range disclosed by the prior art (40:0 – 28:12) is suitable for achieving steady-state blood levels between 0.1 and 1.0, *see* ’740 patent, col. 10:1-2, which is not a considerable difference.

169. A skilled artisan would understand that doxycycline delivered by IR and DR dosages can have equivalent rate and extent of absorption.

170. There is no evidence that ratios between 27:13 – 0:40 (IR:DR) would fail to achieve steady-state blood levels between 0.1 μg/ml and 1.0 μg/ml.

171. There is no evidence that the 30:10 (IR:DR) ratio is critical to achieving steady-state blood levels of doxycycline between 0.1 μg/ml and 1.0 μg/ml.

172. The patentee’s selection of the 75:25 (or 30:10) IR:DR formulation appear to be motivated by considerations other than therapeutic.

173. In selecting a ratio for further development, Shire’s team proposed that the decision be driven by clinical, patent, and manufacturing considerations.

174. There is no evidence that indicates that a 30:10 formulation is more effective clinically than any other ratios or that Galderma and CollaGenex selected the 30:10 formulation for development over other potential ratios based on clinical considerations.

175. Dr. Bergstrom conducted *in silico* modeling with 40 mg doxycycline formulations comprised of various ratios of IR and DR components, which shows that the 30:10 ratio claimed by the Chang patents is not critical to achieving steady-state blood levels.

176. Every 40 mg formulation that Dr. Bergstrom modeled, including 100% IR and 100% DR, shows that they are capable of achieving steady-state blood levels of a minimum of 0.1 μg/ml to a maximum of 1.0 μg/ml.

177. Dr. Bergstrom's experiments shows that any 40 mg doxycycline formulation could achieve steady-state blood levels of a minimum of 0.1 μg/ml to a maximum of 1.0 μg/ml in some subjects.

178. The '572 patent and the '932 application each expressly disclose a "composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline."

179. The '572 patent and the '932 application discloses this limitation inherently.

180. The '572 and the '932 application each disclose administering doxycycline once-a-day to achieve steady state serum concentrations between 0.1 μg/ml to 0.8 μg/ml., more preferably between 0.4 and 0.7 μg/ml.

181. The '572 patent and the '932 application teach that describing the administered amount of drug by serum concentrations or daily dose is interchangeable. *See* '572 patent, col. 5:62-64; '932 app., 8:30-31.

182. During the prosecution of the '240 application, which claims priority to the '854 application, Galderma represented to the PTO that the recitation of a drug serum level is a "more accurate description of a doxycycline dose than dose the amount of doxycycline placed into a capsule." Williams Decl. ¶ 3.

183. Galderma further represented to the PTO that "a skilled artisan would be able to readily deduce what administered dose would provide serum levels of about 0.4 to 0.8 μg/ml doxycycline." Williams Decl. ¶ 4.

184. Thus, the '572 patent and '932 application's disclosure of compositions that achieve steady-state blood levels in the range of about 0.1 μg/ml. to 0.8 μg/ml. is necessarily a disclosure of a composition with 30:10 (IR:DR) formulation because a skilled artisan could readily deduce and immediately recognize from the recited blood levels what ratios of IR:DR would achieve those blood levels.

185. The '854 application (*see, e.g.*, p. 12:12-18) discloses that that the doxycycline composition can be in the form of particles (*e.g.* pellets) and that the composition can have particles with different release profiles.

(iii) "and optionally, (iii) one or more pharmaceutically acceptable excipients."

186. The '572 patent and the '932 application disclose several examples of pharmaceutically acceptable excipients. *See* '572 patent, col. 9:3-10; '932 app., p. 14:30 – p. 15:4.

187. The '572 patent (or the '932 application) discloses a pharmaceutical composition with each of the limitations of Claim 1 of each patent as arranged in the claims.

(b) Method of Treating Claims (Claims 15, 16 of the '532 Patent; Claims 19, 20 of the '740 Patent)

188. Claim 15 of the '532 patent and claim 19 of the '740 patent further recite ***"[a] method for treating rosacea in a mammal in need thereof, comprising administering an oral pharmaceutical composition."***

189. The only difference between these claims and claim 1 of each patent discussed above is that these claims recite that the composition of claim 1 is used in a "method of treating rosacea in a mammal."

190. Claim 16 of the '532 patent and claim 20 of the '740 patent further recites ***"wherein the mammal is a human."***

191. The '572 patent and the '932 application each disclose the method of administering 40 mg of doxycycline once-daily for the treatment of rosacea in humans. *See, e.g.*, '572 patent, col. 9:37-41, col. 34:1-27; '932 app., 16:1-2, 53:3-14, 55:7-19.

(c) Process of Preparing Claims (Claim 20 of the '532 Patent; Claim 22 of the '740 Patent)

192. Claim 20 of the '532 patent and claim 22 of the '740 patent further recite ***"[a] process for preparing an oral pharmaceutical composition"*** and ***"[a] process for preparing a once-daily oral pharmaceutical composition"*** respectively.

193. The '572 patent (*see, e.g.*, col. 8:64 - col. 9:2) and the '932 application (*see, e.g.*, p. 14:25-29) disclose processes of preparing the oral pharmaceutical composition.

(d) Pellet and Dosage Form Dependent Claim Limitations (Claims 2-3 and 17 of the '532 Patent; Claims 6-7, and 10 of the '740 Patent)

194. Claim 2 of the '532 patent recites ***"the IR portion is in the form of pellets,"*** claim 7 of the '740 patent recites ***"a dosage form of a combination of pellets."***

195. For the reasons described above with respect to claims 1, 15, and 20 of the '532 patent, the '854 application as incorporated by reference into the '572 patent and the '932 application discloses the pellets limitation of these claims.

196. Claims 3 and 17 of the '532 patent recites that ***"the pellets are contained in a capsule."***

197. The ‘854 application (s*ee, e.g.*, p.12:12-18) teaches that the composition may be in a capsule.

198. Claim 6 of the ’740 patent recites that the composition is in the form of ***“a granule, tablet, pellet, powder, sachet, capsule, gel, dispersion or suspension”*** and claim 10 recites ***“the DR formulation is in the form of granules, pellets, or tablet.”***

199. The ’572 patent (*see, e.g.*, col. 8:52-56) and the ’932 application (*see, e.g.*, p. 14:14-17) each discloses that the composition may be in the form of a tablet, capsule, and other dosage forms.

(e) Steady State Dependent Claim Limitations (Claims 4, 18 of the ’532 Patent; Claims 2, 21 of the ’740 Patent)

200. Claim 4 of the ’532 patent and claim 2 of the ’740 patent further recites ***“steady state blood levels of the doxycycline of between 0.3 μg/ml to 0.8 μg/ml”*** and claim 18 of the ’532 patent and claim 21 of the ’740 patent correspondingly recite a method of treating rosacea with a composition achieving that steady state blood level.

201. The ’572 patent (or the ’932 application) discloses a pharmaceutical composition that, expressly or inherently, has the additional limitations of claims 4 and 18 of the ’532 patent and claims 2 and 21 of the ’740 patent.

202. The ’572 patent (*see, e.g.*, col. 6:55-58) and ’932 application (s*ee, e.g.*, 10:27-29) disclose preferred serum concentrations of doxycycline between 0.4 μg/ml. to 0.7 μg/ml.

203. Thus, the ’572 patent and the ’932 application disclose pharmaceutical compositions that will give steady-state blood levels of doxycycline between 0.3 μg/ml to 0.8 μg/ml and likewise teach the method of administering such compositions.

(f) Ratio of IR:DR Dependent Claim Limitation (Claim 5 of the '740 Patent)

204. Claim 5 of the '740 patent recites the further limitation ***"wherein the ratio of IR to DR is 75:25."***

205. As set forth above, the '572 patent and the '932 application each disclose, expressly and/or inherently, a pharmaceutical composition comprising 30 mg IR and 10 mg DR.

(g) Excipient Dependent Claim Limitations (Claims 5-8, 19, 21 of the '532 Patent; Claims 8, 9, 11-15 of the '740 Patent)

206. The '572 patent (or the '932 application) discloses a pharmaceutical composition that, expressly or inherently, has the additional limitation of Claims 5-8 and 19 of the '532 Patent and claims 8 and 11-15 of the '740 Patent.

207. Claim 8 of the '740 patent depends from claim 1 and further recites ***"the DR portion comprises at least one enteric polymer."***

208. The '854 application disclose DR coatings including enteric polymers, particularly disclosing "delayed release agents [which] include, but are not limited to, polymeric or biodegradable coatings or matrices, including cellulose polymers, and combinations thereof." S*ee*, '854 app. p. 11:4-9.

209. Claim 9 of the '740 patent depends from claim 8 and further recites:

> wherein the enteric polymer is cellulose acetate phthalate; hydroxypropyl methylcellulose phthalate; polyvinyl acetate phthalate; hydroxypropyl methylcellulose acetate succinate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; cellulose acetate succinate; cellulose acetate hexahydrophthalate; cellulose propionate phthalate; a copolymer of methylmethacrylic acid and methyl methacrylate; a copolymer of methyl acrylate, methylmethacrylate and methacrylic acid; a copolymer of methylvinyl ether and maleic anhydride; ethyl methyacrylate -methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer; zein; shellac; poly(methacylic acid-co-ethyl acrylate) 1:1, or combinations thereof.

210. The ‘854 application discloses DR coatings including enteric polymers, particularly disclosing “delayed release agents [which] include, but are not limited to, polymeric or biodegradable coatings or matrices, including cellulose polymers, and combinations thereof.” *See*, ‘854 app., 11:4-9.

211. This reference to cellulose polymers used as delayed-release agents would be understood by a skilled artisan to be a reference to small class of pH dependent cellulose coatings, which would necessarily include cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate; and cellulose propionate phthalate.

212. Claim 11 of the ’740 patent depends from claim 1 and further recites ***“one or more pharmaceutically acceptable excipients is incorporated in the IR portion, the DR portion, or both.”***

213. The ’932 application (*see, e.g.*, p. 14:30 -15:4) and the ’572 patent (*see, e.g.*, col. 9:3-10) disclose the use of an excipient in the composition.

214. This is also disclosed in the ‘854 application (*see, e.g.*, p. 10:23-26, and p. 14:5-28), which is incorporated by reference.

215. Claim 19 and 21 of the ’532 patent and claim 12 of the ’740 patent recites the additional limitation that ***“one or more pharmaceutically acceptable excipients is a binder, a disintegration agent, a filling agent, a surfactant, a solubilizer, a stabilizer, and combinations thereof.”***

216. The ’572 patent and the ’932 application each disclose the use of filing agents (lactose), disintegration agents (cornstarch), and stabilizers. *See, e.g.*, ’572 patent , col. 9:3-10, 9:21-24; ’932 app., p. 14:30 – p. 15:4, p. 15:15-17.

217. The ‘854 application discloses the use of a surfactant and a binder, which is incorporated by reference by the ’572 patent and the ’932 application. *See, e.g.*’854 app., p. 10:25-26, p.14:5-10.

218. The ’572 patent and the ’932 application disclose the commercial product Periostat® Tablet as a preferred embodiment, which is an inherent disclosure of its inert ingredients, including: hydroxypropylmethlcellulose, lactose, and microcrystalline cellulose. *See* ’572 patent, col. 6:19-23; ’932 app., p. 9:22-25.

219. Claim 6 of the ’532 patent and claim 13 of the ’740 patent recite the additional limitation that ***“the binder is selected from the group consisting of methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and polyvinylpyrrolidone/vinyl acetate copolymer.”***

220. The ‘854 application (*see, e.g.,* p. 14:12-17) discloses the use of the binder methylcellulose.

221. The ’572 patent and the ’932 application inherently disclose the use of hydroxypropyl methlcellulose (a binder) through their disclosure of Periostat® Tablets as a preferred embodiment. *See* ’572 patent, col. 6:19-23; ’932 app., p. 9:22-25.

222. Claim 7 of the ’532 patent and claim 14 of the ’740 patent recite the additional limitation that ***“the disintegration agent is selected from the group consisting of cornstarch, pregelatinized starch, cross-linked carboxymethylcellulose, sodium starch glycolate, and cross-linked polyvinylpyrrolidone.”***

223. The ’572 patent (*see, e.g.,* col. 9:3-6) and the ’932 application disclose *(see, e.g.,* p. 14:30 – 15:2) the use of cornstarch in the composition.

224. Claim 8 of the ’532 patent and claim 15 of the ’740 patent recite the additional limitation that ***“the filling agents are selected from the group consisting of lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, and polyethylene glycol.”***

225. The ’572 patent (*see, e.g.*, col. 9:3-6) and the ’932 application (*see, e.g.*, p. 14:30-15:4) discloses the use of lactose in the composition.

2. The ’572 Patent or the ’932 Application Alone Renders Obvious All Asserted Claims of the Patents-in-Suit

226. Each limitation of claims 1, 2, 5-15, and 19-22 of the ’740 patent and claims 1-8 and 15-21 of the ’532 patent would have been obvious to one of skill in the art over either reference alone.

227. The ’572 patent alone or the ’932 application alone render obvious the limitation of a doxycycline formulation having 30 mg IR and 10 mg DR portions.

228. As set forth above, the ’572 patent claims, and therefore necessarily discloses, the once-daily administration of 40 mg of doxycycline to achieve steady state drug serum concentrations between 0.1 μg/ml and 0.8 μg/ml.

229. The ’932 application contains the same relevant disclosures.

230. The ’572 patent and the ’932 application, through their incorporation by reference of the ‘854 application, expressly disclose the benefits of once-daily dosing. *See* ‘854 app., p. 6:15 – p. 7:12.

231. Thus, the ’572 patent and the ’932 application provide an express motivation to a skilled artisan to formulate 40 mg of doxycycline into a once-daily product.

232. A skilled artisan seeking to formulate a composition described by Claim 26 of the '572 patent or Application Claim 21 of the '932 application would have had a finite and predictable number of options readily available.

233. The first option would be simply to administer 40 mg of doxycycline once-daily in immediate release form.

234. As it is an inherent property of 40 mg of doxycycline administered in immediate release form once-daily that it will achieve steady-state blood levels between 0.1 and 1.0 μg/ml., a skilled artisan would reasonably expect such a formulation to be successful.

235. This property is evinced by both the Periostat® NDA as well as the Periostat® Approval Package, which both report steady-state pharmacokinetic results for 40 mg of doxycycline administered once-daily in immediate release form.

236. Another option that a skilled artisan would consider would be to administer 40 mg of doxycycline using a modified-release approach.

237. The three principles alternatives to an immediate release dosage form would be a delayed-release mechanism, a sustained release mechanism, or a combination of immediate release, delayed-release and/or sustained-release mechanisms.

238. However, a skilled artisan would immediately recognize that a sustained release mechanism is unnecessary for doxycycline because of its long-half and also because it was known at the time that doxycycline is primarily absorbed from upper gastrointestinal tract.

239. Thus, a skilled artisan would be motivated to select either a DR release approach or a combination of IR and DR for a modified release system.

240. A skilled artisan would expect a delayed-release formulation to be a viable option because there was at least one commercial delayed-release doxycycline formulation on the market (*e.g.*, Doryx®).

241. It was known in the art that doxycycline administered through a delayed-release formulation can have, on average, the same rate and extent of absorption as doxycycline administered in immediate release form.

242. A Galderma PK study comparing 40 mg (IR) to its 30:10 (IR:DR) formulation found overall doxycycline absorption to be comparable between the two formulations. *See* GLD00004538-5132, at 4548.

243. Thus, a skilled artisan would reasonably expect that 40 mg of doxycycline, formulated as a delayed-release only formulation, would also achieve steady-state blood levels between 0.1 μg/ml and 1.0 μg/ml.

244. A third option a formulator would immediately recognize is that he could administer 40 mg of doxycycline in a combination of IR and DR forms and also achieve steady-state blood levels between 0.1 μg/ml and 1.0 μg/ml.

245. So long as at least 20 mg of doxycycline is administered in immediate release form a skilled artisan would reasonably expect that the formulation would achieve steady-state blood levels between 0.1 μg/ml and 1.0 μg/ml.

246. Selecting the precise ratio of IR to DR would be a question of routine optimization and experimentation that are well within the ability of a skilled artisan.

247. Although any ratio of IR:DR would be expected to achieve steady-state blood levels between 0.1 and 1.0 μg/ml., a skilled artisan would be motivated to formulate a greater portion of the doxycycline in the immediate-release portion for several reasons.

248. First, delayed-release dosage forms are more susceptible to inter-subject and intra-subject variability due to gastrointestinal transit times and pH differences.

249. By placing more of the doxycycline into the immediate release portion, a formulator would reduce the risk of such variability.

250. Second, the ’572 patent and the ’932 application, through their incorporation by reference of the ‘854 application, expressly teach that at least 50% and more preferably 80% of the drug should be released in the upper gastrointestinal tract.

251. This is consistent with the absorption window of doxycycline known to artisans at the time.

252. Third, a skilled artisan would also select a higher portion to be formulated into the IR portion because of manufacturing and cost considerations.

253. Fourth, because the ’572 patent and the ’932 application express a preference for blood levels between 0.4 μg/ml and 0.7 μg/ml, this provides additional reason to place more of the doxycycline into the immediate release portion to ensure these blood levels are achieved.

254. One of the ratios that would be obvious to try is 30:10 (IR:DR).

255. This specific ratio would be obvious for practical reasons.

256. In developing a formulation a person of ordinary skill would select three to four options and then conduct either *in vitro, in silico,* or *in vivo* testing with each of those options.

257. The obvious choices in this context would be to select ratios that would cover the range of potential ratios. In this case, the obvious options for IR:DR combinations would 30:10 mg (IR:DR), 20:20 (IR:DR), and 10:30 (IR:DR).

258. Second, a skilled artisan would be motivated to select ratios that would be reliably reproducible on the commercial scale. For example, a ratio of 39:1 (IR:DR) would be

theoretically possible but would present greater challenges from a manufacturing standpoint to ensure that each dosage form met content uniformity requirements.

259. A skilled artisan would reasonably expect that any of these formulations would achieve blood levels between 0.1 μg/ml and 1.0 μg/ml.

260. A skilled artisan's expectation of success is supported by the high level of predictability for formulating doxycycline formulations.

261. At the time of the filing of the applications that issued as the patents-in-suit, there were both immediate and delayed release doxycycline formulations on the market including formulations that administered doses between 20 and 50 mg of doxycycline

262. The asserted claims of the patents-in-suit are directed to a combination of familiar elements, produced according to known methods that yield no more than predictable results.

263. Immediate and delayed release doxycycline formulations were commercially available and well-known prior to the priority date of the patents-in-suit.

264. The absorption properties of doxycycline were also well known, including the absorption properties of doxycycline at low-doses.

265. It was also well known that one way to achieve once-daily dosing of a product would be through a delivery system containing portions with different release profiles.

266. It was also known in the art that doxycycline serum concentrations between 0.1 μg/ml and 1.0 μg/ml. was a desirable therapeutic profile.

267. There were no teachings in the art that would suggest that doxycycline could not be administered once-daily or that IR:DR formulations of doxycycline were unsuitable.

268. The art specifically taught such combinations.

269. Arriving at a suitable ratio of IR to DR portions would be require only routine skill and experimentation for a formulator with experience in controlled-release drug delivery.

270. And, for the reasons stated above, Claims 2, 5-16, and 19-22 if not anticipated would also be obvious in view of the '932 application or the '572 patent.

3. The '572 Patent or the '932 Application, in View of the '748 Patent, Renders Obvious All Asserted Claims of the Patents-in-Suit.

271. Claims 1-8 and 15-21 of the '532 patent and claims 1-2, 5-15, and 19-22 would have been obvious to one of ordinary skill in the art over the '572 patent or the '932 application in view of the '748 patent.

272. The '748 patent is directed to once-daily delivery systems for minocycline, which is second-generation tetracycline that has similar properties to doxycycline.

273. The '748 patent explains that its object is "a once-a-day delivery system which maintains therapeutic blood level concentrations of the medicament in a patient for twenty-four hours." '748 patent, col. 1:12-15.

274. The '748 patent discloses formulations that include a pulsed-release formulation comprised of a major portion of a first pulse of quick release granules and a minor portion of a second pulse of coated granules. *Id.* at col. 1:17-22.

275. In particular, the '748 patent discloses that improved bioavailability can be achieved by "increasing the ratio of quick release initial loading pellets to slow release secondary loading coated pellets and by using a modified coating composition for the latter." *Id.*, col. 3:48-52. The "secondary loading pellets" are coated with a pH-sensitive coating, *id.*, col. 3: 55-58—*i.e.*, an enteric polymer.

276. The '932 application and the '572 patent each identify minocycline and doxycycline as tetracyclines suitable for use in low dose tetracycline treatments.

277. Because both doxycycline and minocycline have long half-lives and similar known absorption windows, a prior art once-daily minocycline formulation would be a logical reference that a skilled artisan would consider when seeking to formulate a once-daily doxycycline treatment.

(a) Claim 1 of the '532 Patent and Claim 1 of the '740 Patent

278. As described above and as set forth below, the '572 patent in combination with the '748 patent (or the '932 application in combination with the '748 patent) discloses, teaches, and suggests pharmaceutical compositions with each of the limitations of Claim 1 as arranged in the claim.

(i) An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml,

279. As set forth above, the '572 patent and the '932 application expressly discloses oral pharmaceutical compositions of doxycycline that will give steady state blood levels of a minimum of 0.1 µg/ml. and a maximum of 1.0 µg/ml.

280. The '748 patent discloses minocycline, rather than doxycycline, but it discloses an oral pharmaceutical composition that will desired steady-state blood levels after once-daily dosing.

281. The '748 patent is directed to formulations that maintain blood levels in the therapeutic range for up to 24 hours. *See* '748 patent, col. 1:28-37.

282. Although the '748 patent reports that it could be used to deliver doses as low as 25 mg, *see id.*, col. 8:11-16, which is well under the level that the '572 patent and the '932 application teach would be a non-antibiotic dose of doxycycline. *See* '572 patent, col. 6:9-13; '932 application, 9:12-15.

(ii) the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline (claim 1 of the '740 patent) / (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with at least one enteric polymer (claim 1 of the '532 patent);

283. The '748 patent teaches that desired drug serum levels can be achieved through a once-daily two-pulse delivery systems. '748 patent, col. 3:19-30.

284. The first pulse is delivered through quick release (*i.e.* IR) granules and the second pulse is delivered through coated granules that provide a delayed release.

285. The '748 patent discloses that improved bioavailability can be achieved by "increasing the ratio of quick release initial loading pellets to slow release secondary loading coated pellets and by using a modified coating composition for the latter." *Id.*, col. 3:48-52.

286. The "secondary loading pellets" are coated with a pH-sensitive coating, *Id.*, col. 3:55-58—*i.e.* an enteric polymer.

287. Thus, the '748 patent expressly discloses dosage forms with IR and DR portions as claimed by the '740 patent.

288. The '748 patent also discloses a range of ratios that would be effective to maintain blood levels at the desired therapeutic range. Those ratios range from 51:49 to 80:20. '748 patent, col. 8:16-24; *see also* col. 5:11-21. Claim 1 of the '740 patent's ratio of 30:10 (*i.e.* 75:25) is within this range disclosed by the '748 patent.

289. The '748 patent discloses the use of coated spheres (*i.e.* pellets), *see* col. 9:58-60, and the use of a combination thereof as described above.

290. In addition, the ’748 patent provides reason to use IR and DR forms of doxycycline with a ratio of IR:DR of greater than 1, teaching that bioavailability can be improved by increasing the ratio of IR pellets to DR pellets.

291. One of ordinary skill in the art would also have had a reason and would have been motivated to increase the relative amount of IR to DR portions of doxycycline, in view of the known interchangeability of the two tetracyclines as taught by the ’572 patent and the ’932 application, and the preferential absorption of both minocycline and doxycycline in the upper GI tract.

292. A skilled artisan would view minocycline and doxycycline as comparable and as overlapping to a considerable extent.

293. Thus, a skilled artisan would have reason and motivation to substitute doxycycline for minocycline in the composition described in the ’748 patent.

294. Because it was known that doxycycline is absorbed in the upper gastrointestinal tract and has a very long half life, a skilled artisan would appreciate that the compositions disclosed in the ’748 patent could be successfully modified to achieve the once-daily and sustained-release compositions taught by the ’572 patent and the ’932 application.

295. One of ordinary skill in the art would also have been motivated to modify the teachings of the ’748 patent to provide a low dose of doxycycline as taught by the ’572 patent/’932 application in order to avoid reduction of healthy flora in the body, the reduction of antibiotic resistant organisms, and the overgrowth of opportunistic yeast and fungi, and to select an amount of IR pellets that is greater than the amount of the DR pellets, including a 40 mg dose containing a 3:1 ratio of IR and DR pellets (*i.e.* containing 30 mg of minocycline in IR pellets and 10 mg minocycline in DR pellets).

296. The ’748 patent also discloses techniques for how to modify a twice-daily formulation to achieve once-daily dosing.

297. In Comparative Example IA, the ’748 patent discloses the administration of 50 mg of immediate release minocycline hydrochloride twice daily to human subjects. *See* ’748 patent, col. 13:21-45.

298. The plasma levels achieved with the immediate release minocycline are then used to compare and evaluate the bioavailability of the once-daily minocycline formulations. *See* ’748 patent, Fig. 5; col. 16:63-18:16.

299. A skilled artisan would have had reason to prepare an oral pharmaceutical composition comprising 40 mg doxycycline with a ratio of IR:DR portions of greater than 1, *e.g.* about 30 mg doxycycline in an IR formulation and about 10 mg doxycycline in a DR portion and would have a reasonable expectation of success in achieving the desired steady state blood levels of doxycycline of a minimum of 0.1 µg/ml. and a maximum of 1.0 µg/ml.

(iii) “and optionally, (iii) one or more pharmaceutically acceptable excipients.”

300. The ’748 patent disclose several examples of pharmaceutically acceptable excipients. *See* ’748 patent, col. 8:65 – col 10:45, col 11:3-26.

301. The ’572 patent in view of the ’748 patent (or the ’932 application in view of the ’748 patent) discloses, teaches, and suggests a pharmaceutical composition with each of the limitations of Claim 1 as arranged in the claim.

(b) Method of Treating Claims (Claims 15, 16 of the '532 Patent; Claims 19, 20 of the '740 Patent)

302. Claim 15 of the '532 patent and claim 19 of the '740 patent further recite ***"[a] method for treating rosacea in a mammal in need thereof, comprising administering an oral pharmaceutical composition."***

303. For the reasons set forth above, the '748 patent in combination with the '572 patent (or the '932 application) discloses a method for treating rosacea in a mammal with a composition comprising doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml. and a maximum of 1.0 μg/m.l, the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients.

304. Claim 16 of the '532 patent and claim 20 of the '740 patent further recites ***"wherein the mammal is a human."***

305. The '748 patent discloses methods of administering pharmaceutical compositions to human subjects. *See, e.g.*, '748 patent, col. 16:63 – 18:16.

(c) Process of Preparing Claims (Claim 20 of the '532 Patent; Claim 22 of the '740 Patent)

306. Claim 20 of the '532 patent and claim 22 of the '740 patent further recite ***"[a] process for preparing an oral pharmaceutical composition"*** and ***"[a] process for preparing a once-daily oral pharmaceutical composition"*** respectively.

307. For the reasons set forth above, the '748 patent in combination with either the '572 patent or the '932 application discloses a composition doxycycline comprising, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml.

and a maximum of 1.0 μg/ml., the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients.

(d) The '748 Pellet and Dosage Form Dependent Claim Limitations
(Claims 2-3 and 17 of the '532 Patent; Claims 6-7, and 10 of the '740 Patent)

308. Claim 2 of the '532 patent recites ***"the IR portion is in the form of pellets,"*** claim 7 of the '740 patent recites ***"a dosage form of a combination of pellets."***

309. The '748 patent discloses the use of coated spheres (*i.e.*, pellets), *see* col. 9:58-60, and the use of a combination thereof as described above.

310. Claims 3 and 17 of the '532 patent recites that ***"the pellets are contained in a capsule."***

311. The '748 patent teaches that the disclosed uncoated and coated spheres or granules can be filled into capsules, and that such capsules can be administered in a method of treating. *See, e.g.,* '748 patent, col. 5:22-27.

312. Claim 6 of the '740 patent recites that the composition is in the form of ***"a granule, tablet, pellet, powder, sachet, capsule, gel, dispersion or suspension"*** and claim 10 recites ***"the DR formulation is in the form of granules, pellets, or tablet."***

313. The '748 patent discloses that the DR portion can be in the form of granules or coated spheres (*i.e.*, pellets). *See* col. 9:58-60.

314. The '748 patent discloses that the disclosed compositions could be filled into capsules. *See* '748 patent, col. 11:66 -12:8.

315. The '748 patent also discloses processes for preparing same. *See, e.g.,* '748 patent, col. 13:47 – col. 15:66.

(e) Steady State Dependent Claim Limitations (Claims 4, 18 of the '532 Patent; Claims 2, 21 of the '740 Patent)

316. Claim 4 of the '532 patent and claim 2 of the '740 patent further recites ***"steady state blood levels of the doxycycline of between 0.3 μg/ml to 0.8 μg/ml"*** and claim 18 of the '532 patent and claim 21 of the '740 patent correspondingly recite a ***method of treating rosacea with a composition achieving that steady state blood level***.

317. For the reasons set forth above, it would be obvious to modify the formulations disclosed by the '748 patent to achieve the steady-state blood levels of 0.4 μg/ml to 0.7 μg/ml as taught by the '572 patent or the '932 application.

318. When coupled with the disclosure of the '572 patent (or the '932 application), this combined disclosure renders Claim 4 of the '532 patent and Claim 2 of the '740 patent obvious.

319. For the reasons set forth above, the '748 patent in combination with the '572 patent (or the '932 application) discloses methods of administering pharmaceutical compositions that will give steady-state blood levels of doxycycline between 0.3 μg/ml. to 0.8 μg/ml.

(f) Ratio of IR:DR Dependent Claim Limitation (Claim 5 of the '740 Patent)

320. Claim 5 of the '740 patent recites the further limitation ***"wherein the ratio of IR to DR is 75:25."***

321. The '572 patent and the '932 application each disclose, expressly and/or inherently, a pharmaceutical composition comprising 30 mg IR and 10 mg DR.

(g) Excipient Dependent Claim Limitations (Claims 5-8, 19, 21 of the '532 Patent; Claims 8, 9, 11-15 of the '740 Patent)

322. Claim 8 of the '740 patent depends from claim 1 and further recites ***"the DR portion comprises at least one enteric polymer."***

323. The ’748 patent discloses several pH sensitive enteric polymers that are suitable for use in its DR portion. *See, e.g.,* ’748 patent, col. 10:56-11:26.

324. Claim 9 of the ’740 patent depends from claim 8 and further recites:

> wherein the enteric polymer is cellulose acetate phthalate; hydroxypropyl methylcellulose phthalate; polyvinyl acetate phthalate; hydroxypropyl methylcellulose acetate succinate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; cellulose acetate succinate; cellulose acetate hexahydrophthalate; cellulose propionate phthalate; a copolymer of methylmethacrylic acid and methyl methacrylate; a copolymer of methyl acrylate, methylmethacrylate and methacrylic acid; a copolymer of methylvinyl ether and maleic anhydride; ethyl methyacrylate -methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer; zein; shellac; poly(methacylic acid-co-ethyl acrylate) 1:1, or combinations thereof.

325. The ’748 patent discloses at least the following enteric polymers: copolymer of methylmethacrylic acid and methyl methacrylate; cellulose acetate phthalate; polyvinyl acetate phthalate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; hydroxypropyl methylcellulose phthalate. *See* ’748 patent, col.11:5-26.

326. When coupled with the disclosure of the ’572 patent (or the ’932 application), this combined disclosure renders claim 9 obvious.

327. Claim 11 of the ’740 patent depends from claim 1 and further recites ***“one or more pharmaceutically acceptable excipients is incorporated in the IR portion, the DR portion, or both.”***

328. The ’748 patent discloses that both the IR and DR portions contain pharmaceutically acceptable excipients. *See, e.g.,* ’748 patent, col. 4:33 – 5:21.

329. Claim 19 and 21 of the ’532 patent and claim 12 of the ’740 patent recites the additional limitation that ***“one or more pharmaceutically acceptable excipients is a binder, a disintegration agent, a filling agent, a surfactant, a solubilizer, a stabilizer, and combinations thereof.”***

330. The ’748 patent discloses a number of well-known binders, disintegration agents, and filing agents, and stabilizers. *See, e.g.,* ’748 patent, col. 8:65-9:18, col. 11:66 – 12:8.

331. Claim 6 of the ’532 patent and claim 13 of the ’740 patent recite the additional limitation that ***“the binder is selected from the group consisting of methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and polyvinylpyrrolidone/vinyl acetate copolymer.”***

332. The ’748 patent discloses the use of several well-known binders, including specifically the following: hydroxyethyl cellulose; polyvinylpyrrolidone; and hydroxypropyl methylcellulose. *See* ’748 patent, col. 8:65 - 9:18.

333. Claim 7 of the ’532 patent and claim 14 of the ’740 patent recite the additional limitation that ***“the disintegration agent is selected from the group consisting of cornstarch, pregelatinized starch, cross-linked carboxymethylcellulose, sodium starch glycolate, and cross-linked polyvinylpyrrolidone.”***

334. The ’748 patent discloses the use of well-known disintegration agents, including starch and pregelatinzed starch. *See, e.g.,*’748 patent, col. 8:5 – 9:18.

335. Claim 8 of the ’532 patent and claim 15 of the ’740 patent recite the additional limitation that ***“the filling agents are selected from the group consisting of lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, and polyethylene glycol.”***

336. The ’748 patent discloses the use of well-known filing agents, including lactose and microcrystalline cellulose. *See, e.g.,* ’748 patent, col. 8:65 – 9:18.

C. The Asserted Claims of the Patents-in-Suit are Invalid In View of the '106 Application or, in the Alternative, the '240 Application

1. The '106 Application or the '240 Application Anticipates claims 1-8 and 20-21 of the '532 Patent and Claims 1, 2, 5-15, and 22 of the '740 Patent

337. Each limitation of claims 1-8 and 20-21 of the '532 patent and claims 1, 2, 5-15, and 22 of the '740 patent are disclosed, expressly and/or inherently, by the '106 application.

338. Each limitation of claims 1-8 and 20-21 of the '532 patent and claims 1, 2, 5-15, and 22 of the '740 patent are also disclosed, expressly and/or inherently, by the '240 application.

339. Because the written descriptions contained in the '106 application and the '240 application are identical in all material respects, reference to either includes the other, but does not mean a combination of the references.

(a) Claim 1 of the '532 Patent and Claim 1 of the '740 Patent

340. As described above and as set forth below, the '106/240 applications disclose, expressly or inherently, each of the limitations of Claim 1 as arranged in the claim.

(i) An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml,

341. The '106/'240 applications disclose oral pharmaceutical compositions of doxycycline that will give steady state blood levels of a minimum of 0.1 µg/ml. and a maximum of 1.0 µg/ml., preferably between 0.3 and 0.8 µg/ml. *See, e.g.*, '106 app., 4:15 – 5:26, 18:1-30.

342. The serum concentrations recited by the '106 /240 applications are based on steady state pharmacokinetics. *See, e.g., id*., 13:10-12.

343. The '106/240 applications expressly disclose a number of different dosage forms. *See, e.g.,* '106 app., 11:25 – 16:15.

344. They likewise claim such compositions. *See, e.g.*, 18:1 – 19:25.

345. A skilled artisan would not need to have the precise details of excipients recited in the reference in order to recognize these to be examples of formulations.

346. Galderma sought and obtained allowance of Claim 82 during prosecution of the '240 application.

347. That claim is specifically drawn to a pharmaceutical composition consisting of a capsule comprised of IR and DR beadlets.

348. Galderma, by prosecuting such a claim, represented to the PTO and the public that the '240 application (and necessarily the '106 application) disclosed such subject matter.

> **(ii) the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline (claim 1 of the '740 patent) / (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with at least one enteric polymer (claim 1 of the '532 patent);**

349. The '106/240 applications expressly disclose compositions comprising an IR portion comprising 30 mg of doxycycline and a DR portion comprising 10 mg of doxycycline.

350. This limitation is also inherently disclosed by the 106/240 applications.

351. The '106/240 applications disclose once daily administration of doxycycline compositions that achieve steady-state blood levels between 0.1 and 1.0 μg/ml. *See, e.g.*, '106 app., 4:15 – 5:26.

352. The '106 application describes various approaches for formulating controlled release compositions, but one such approach is through the use of IR and DR agents (*i.e.*, IR and DR portions). *Id.*, 9:31 – 10:2.

353. One of the embodiments disclosed by the '106/240 applications are "polymeric capsules filled with solid particles which can, in turn, by made to release the tetracycline compound according to a known pattern or profile." *Id*., 11:27-29.

354. And "[s]uch particles can also be made to have more than one release profile so that over an extended time the combined release patterns provide a pre-selected profile." *Id*., 11:29-31.

355. The '106/240 applications further specify that "[o]ne embodiment of the unit dosage form is a capsule which contains beadlets." *Id*., 15:20.

356. More specifically, the '106 application explains that "[w]thin each capsule are beadlets which are coated with various coatings that dissolve at different pH levels." *Id*., 15:21-22.

357. The '106 application's disclosure of "capsules with beadlets which are coated with various coatings that dissolve at different pH levels," *id*., 15:21-22, teaches that the dosage form should have a ratio of different beadlets to achieve the desired therapeutic serum concentration levels.

358. When read in light of the '106 applications' disclosure of using combinations of IR and DR agents to achieve the desired therapeutic serum concentrations, a skilled artisan would understand this to mean that one composition disclosed by the '106 application is a capsule containing IR and DR beadlets that are combined in a ratio to achieve the desired therapeutic serum concentrations.

359. The fact that the '106/240 application discloses formulations comprised of IR and DR portions is further confirmed by Galderma's seeking and obtaining allowance of Claim 82.

360. As described above, Claim 82 is directed to a capsule comprised IR and DR beadlets that achieves blood levels between 0.4 μg/ml and 0.8 μg/ml.

361. The '106/240 applications describe the amount of doxycycline administered by the disclosed compositions in terms of drug serum concentrations. *See, e.g., id.* 4:23-31, 13:19-24.

362. The '106/240 applications explain that the "amount administered will vary depending on various factors as is known in the art, such as the size of the mammal, the specific tetracycline used, *etc*.

363. The amount can be determined by one of skill in the art. *Id.*, 13:13-16.

364. Based on the '106/240 applications disclosure of target serum concentrations between 0.4 μg/ml and 0.8 μg/ml.

365. For doxycycline, a skilled artisan would immediately recognize that one such composition should contain a total of 40 mg of doxycycline.

366. Because the '106 application discloses the once-daily administration of doxycycline using IR and DR components, it necessarily discloses the full range of IR and DR ratios to be used with a 40 mg formulation.

367. That range is from 40:0 (IR:DR) to 0:40 (IR:DR).

368. A disclosure of a range is expressly a disclosure of all points within that range.

369. Accordingly, the '106/240 applications expressly disclose the 30:10 (IR:DR) ratio even though it does not use those precise terms.

370. Thus, there is no evidence that the 30:10 (IR:DR) ratio is critical to achieving steady-state blood levels of doxycycline between 0.1 μg/ml and 1.0 μg/ml.

371. Dr. Bergstrom conducted *in silico* modeling with various ratios of IR and DR potions.

372. Every 40 mg formulation that Dr. Bergstrom modeled, including 100% IR and 100% DR, shows that they are capable of achieving steady-state blood levels of a minimum of 0.1 μg/ml to a maximum of 1.0 μg/ml.

373. Dr. Bergstrom's experiments, including 100% IR and 100% DR, shows that they are capable of achieving steady-state blood levels of a minimum of 0.1 μg/ml to a maximum of 1.0 μg/ml.

374. Dr. Bergstrom's experiments confirm that the 30:10 ratio is not critical to achieving the claimed steady-state blood levels.

375. In the absence of any criticality associated with the 30:10 (IR:DR) limitation and the lack of evidence of any considerable difference between the claimed ratio and other points within the disclosed range, the '106 and '240 applications each expressly disclose a "composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline."

376. Even if the '106/240 applications did not expressly disclose this limitation, this limitation is inherently disclosed.

377. As set forth above, the '106/240 applications each discloses administering doxycycline once-a-day to achieve steady state serum concentrations between 0.1 μg/ml to 1.0 μg/ml, more preferably between 0.4 μg/ml and 0.8 μg/ml.

378. During the prosecution of the '240 application, Galderma represented to the PTO that the recitation of a drug serum level is a "more accurate description of a doxycycline dose than dose the amount of doxycycline placed into a capsule." Williams Decl. ¶ 3.

379. It was further represented to the PTO that "a skilled artisan would be able to readily deduce what administered dose would provide serum levels of about 0.4 to 0.8 μg/ml doxycycline." Williams Decl. ¶ 4.

380. Accordingly, the '106/240 applications' disclosure of compositions that achieve steady-state blood levels between 0.1 μg/ml. to 1.0 μg/ml is a disclosure of a composition with 30:10 (IR:DR) formulation because a skilled artisan could readily deduce and immediately recognize from the recited blood levels what ratios of IR:DR would achieve those blood levels.

381. Galderma did not consider a constant rate of release to be part of its invention with respect to the '106/'240 applications.

382. In arguing the patentability of Claim 82 over the prior art, Galderma represented to the PTO that "Claim 82 cannot include a prolonged release agent." AMORA_00132169-173, at 00132172; *see also* AMORA_00132204-2217, at 132209 ("[T]here is no sustained release agent in the claimed composition.").

383. The a skilled artisan would not have understood the compositions of the '106/240 application to require that drug be released at a substantially constant rate as Plaintiffs have previously contended.

(iii) "and optionally, (iii) one or more pharmaceutically acceptable excipients."

384. The '106/240 applications disclose several examples of pharmaceutically acceptable excipients. *See, e.g.*, '106 app., 8:25-28, 10:5-7, 14:1-24.

385. The '106 application (or the '240 application) discloses a pharmaceutical composition with each of the limitations of Claim 1 as arranged in the claim.

(b) Pellet and Dosage Form Limitations (Claims 2-3 and 17 of the '532 Patent; Claims 6-7, and 10 of the '740 Patent)

386. Claim 2 of the '532 patent recites ***"the IR portion is in the form of pellets,"*** claim 7 of the '740 patent recites ***"a dosage form of a combination of pellets."***

387. The '106/240 applications disclose that the doxycycline composition can be in the form of beadlets (*i.e.*, pellets) with different coatings and release profiles. *See, e.g.*, 15:20-22.

388. Claims 3 and 17 of the '532 patent recites that ***"the pellets are contained in a capsule."***

389. The '106/240 applications disclose that the doxycycline composition can be in the form of beadlets with different coatings and release profiles and that such beadlets may be filled in a capsule.

390. Claim 6 of the '740 patent recites that the composition is in the form of ***"a granule, tablet, pellet, powder, sachet, capsule, gel, dispersion or suspension"*** and claim 10 recites ***"the DR formulation is in the form of granules, pellets, or tablet."***

391. The '106/240 application teaches that the composition may be in a tablet, pellet, capsule, or suspension (*see, e.g.* 11:25-27).

392. The '106/240 applications disclose that the doxycycline composition can be in the form of beadlets that dissolve at different pH levels (*see, e.g.*, 15:20-22).

(c) Process of Preparing Limitations (Claim 20 of the '532 Patent; Claim 22 of the '740 Patent)

393. Claim 20 of the '532 patent and claim 22[1] of the '740 patent further recite ***"[a] process for preparing an oral pharmaceutical composition"*** and ***"[a] process for preparing a once-daily oral pharmaceutical composition"*** respectively.

394. Claim 20 of the '532 patent and claim 22 of the '740 patent are directed to a process for preparing an oral pharmaceutical composition comprising doxycycline.

395. The oral pharmaceutical composition recited in these claims have has the same limitations as the oral pharmaceutical composition of claim 1 in their respective patents.

396. Each of the limitations of these claims is anticipated for the reasons discussed above with respect to claim 1.

397. The '106/240 application discloses a process of preparing the oral pharmaceutical composition (described throughout the application). *Id.*, 9:20-23, 14:26-32.

(d) Steady State Limitations (Claims 4 of the '532 Patent; Claims 2 of the '740 Patent)

398. Claim 4 of the '532 patent and claim 2 of the '740 patent further recites ***"steady state blood levels of the doxycycline of between 0.3 µg/ml to 0.8 µg/ml."***

399. The '106/240 applications teach that the composition will give blood levels of the doxycycline of between 0.4 µg/ml to 0.8 µg/ml. *See, e.g., id.,13:20*-24.

(e) Ratio of IR:DR Limitation (Claim 5 of the '740 Patent)

400. Claim 5 of the '740 patent recites the further limitation ***"wherein the ratio of IR to DR is 75:25."***

[1] Claim 22 of the '740 patent recites "the tetracycline" as the active ingredient instead of "doxycycline." Because doxycycline is a species within the tetracycline genus, this is not a material difference for purposes of invalidity.

401. For the reasons set forth above with respect to Claim 1, the '106/240 applications each disclose, expressly and/or inherently, a pharmaceutical composition comprising 30 mg IR and 10 mg DR.

402. As the ratio of IR to DR in such a formulation is 75:25, Claim 5 is anticipated by the '106/240 applications.

(f) Excipient Limitations (Claims 5-8, 21 of the '532 Patent; Claims 8, 9, 11-15 of the '740 Patent)

403. Claim 8 of the '740 patent depends from claim 1 and further recites ***"the DR portion comprises at least one enteric polymer."***

404. The '106/240 applications disclose DR coatings including enteric polymers.

405. In particular, they disclose "delayed release agents [which] include, but are not limited to, polymeric or biodegradable coatings or matrices, including cellulose polymers, and combinations thereof." *Id.*, 10:17-22.

406. The '106/240 application points to the '030 patent for examples of controlled-release agents known in the art. *Id.* at 9:1-5.

407. Among those agents are a number of suitable agents that a skilled artisan would immediately recognize as enteric polymers, including: hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose succinate, polymers and copolymers of (meth)acrylic acid and (meth)acrylic acid methyl ester. *See*, U.S. Patent No. 4,837,030, col. 6:42-64.

408. Claim 9 of the '740 patent depends from claim 8 and further recites:

> wherein the enteric polymer is cellulose acetate phthalate; hydroxypropyl methylcellulose phthalate; polyvinyl acetate phthalate; hydroxypropyl methylcellulose acetate succinate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; cellulose acetate succinate; cellulose acetate hexahydrophthalate; cellulose propionate phthalate; a copolymer of

> methylmethacrylic acid and methyl methacrylate; a copolymer of methyl acrylate, methylmethacrylate and methacrylic acid; a copolymer of methylvinyl ether and maleic anhydride; ethyl methyacrylate -methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer; zein; shellac; poly(methacylic acid-co-ethyl acrylate) 1:1, or combinations thereof.

409. The '106/240 application discloses that DR coatings including enteric (cellulose) polymers (*see, e.g.*, p. 10:17-22).

410. The enteric polymers listed in claim 9 represent a small group of well-known classes of enteric polymers and one of ordinary skill in the art would at once envisage the recited enteric polymers.

411. In particular, it discloses "delayed release agents [which] include, but are not limited to, polymeric or biodegradable coatings or matrices, including cellulose polymers, and combinations thereof." *See*, '106 app, p. 10, 17-22.

412. This reference to cellulose polymers used as delayed-release agents would be understood by a skilled artisan to be a reference to small class of pH dependent cellulose coatings, which would necessarily include cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate; and cellulose propionate phthalate.

413. In addition, the '106/240 application points to the '030 application for examples of controlled-release agents know in the art. *Id.* at 9:1-5.

414. Among those agents are: hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose succinate, polymers and copolymers of (meth)acrylic acid and (meth)acrylic acid methyl ester. *See* U.S. Patent No. 4,837,030, col. 6:42-64.

415. Claim 11 of the ’740 patent depends from claim 1 and further recites ***“one or more pharmaceutically acceptable excipients is incorporated in the IR portion, the DR portion, or both.”***

416. The ’106/240 application discloses the use of an excipient in the composition (*see, e.g.*, 8:25-28, 14:1-24).

417. Claim 21 of the ’532 patent and claim 12 of the ’740 patent recites the additional limitation that ***“one or more pharmaceutically acceptable excipients is a binder, a disintegration agent, a filling agent, a surfactant, a solubilizer, a stabilizer, and combinations thereof.”***

418. The ’106/240 applications disclose the use of binders and surfactants in the composition (*see, e.g.*, p. 14:8-13, 10:4-7).

419. Claim 6 of the ’532 patent and claim 13 of the ’740 patent recite the additional limitation that ***“the binder is selected from the group consisting of methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and polyvinylpyrrolidone/vinyl acetate copolymer.”***

420. The ’106/240 applications disclose the use of the binder methylcellulose composition (*see, e.g.*, 14:8-13).

421. Claim 7 of the ’532 patent and claim 14 of the ’740 patent recite the additional limitation that ***“the disintegration agent is selected from the group consisting of cornstarch, pregelatinized starch, cross-linked carboxymethylcellulose, sodium starch glycolate, and cross-linked polyvinylpyrrolidone.”***

422. The ’106/240 applications disclose the use of starch in the composition (*see, e.g.*, 10:11-13).

423. Claim 8 of the ’532 patent and claim 15 of the ’740 patent recite the additional limitation that ***“the filling agents are selected from the group consisting of lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, and polyethylene glycol.”***

424. The ’106/240 applications disclose the use of starch and dibasic calcium phosphate in the composition (*see, e.g.,* 14:21-24).

2. The ’106 Application or the ’240 Application Alone Renders Obvious Claims 1-8 and 20-21 of the ’532 Patent and Claims 1, 2, 5-15, and 22 of the ’740 Patent

425. The limitations of claims 1-8 and 20-21 of the ’532 patent and claims 1, 2, 5-15, or 22 of the ’740 patent would have been obvious to one of skill in the art over either the ’106 application or the ’240 application alone.

426. The ’106/240 applications disclose and claim the once-daily administration of doxycycline to achieve steady state drug serum concentrations between 0.1 and 1.0 μg/ml and the benefits of such dosing.

427. The ’106/240 applications provide an express motivation to a skilled artisan to formulate doxycycline into a once-daily product to achieve serum concentrations between 0.1 and 1.0 μg/ml.

428. A skilled artisan seeking to formulate a composition described by Application Claim 20 of the ’106 application or Application Claim 82 of the ’240 application would have a finite and predictable number of options readily available to him.

429. A skilled artisan would be motivated to select 40 mg of doxycycline as the dosage amount based on the fact that it was known in the art that 40 mg of doxycycline, administered once-daily in immediate release form, would achieve steady state blood levels between 0.1 and 1.0 μg/ml. *See* Periostat® Approval Package, at AMORA_00257036-7040.

430. The steady-state pharmacokinetics of 40 mg of doxycycline is an intrinsic property of such a dosage form and readily ascertainable by a skilled artisan even if the Periostat® Approval Package did not disclose these characteristics.

431. It would be obvious to a skilled artisan that 40 mg of doxycycline could be administered in immediate release form only and achieve the blood levels described by the '106/240 applications.

432. Another option that a skilled artisan would consider would be to administer 40 mg of doxycycline using a modified-release approach.

433. The three principle alternatives to an immediate release dosage form would be a delayed-release mechanism, a sustained release mechanism, or a combination of immediate release, delayed-release and/or sustained-release mechanisms.

434. A skilled artisan would recognize that a sustained release mechanism is unnecessary for doxycycline because of its long-half and also because it was known at the time that doxycycline is primarily absorbed from upper gastrointestinal tract.

435. A skilled artisan would be motivated to select either a DR release approach or a combination of IR and DR.

436. A skilled artisan would expect a delayed-release formulation to be a viable option because there was at least one commercial delayed-release formulation on the market (Doryx®).

437. It was known in the art that doxycycline administered through a delayed-release formulation can have, on average, the same rate and extent of absorption as doxycycline administered in immediate release form. *See* Williams et al., at 104.

438. Thus, a skilled artisan would reasonably expect that 40 mg of doxycycline, formulated as a delayed-release only formulation, would also achieve steady-state blood levels between 0.1 and 1.0 μg/ml.

439. A third option a formulator would immediately recognize is that he could administer 40 mg of doxycycline in a combination of IR and DR forms and also achieve steady-state blood levels between 0.1 and 1.0 μg/ml.

440. So long as at least 20 mg of doxycycline is administered in immediate release form a skilled artisan would expect that the formulation would achieve steady-state blood levels between 0.1 and 1.0 μg/ml. *See* Periostat® Approval Package, at AMORA_00257036-7040.

441. Selecting the precise ratio of IR to DR would be simply a question of routine optimization and experimentation that are well within the ability of a skilled artisan.

442. A skilled artisan would be motivated to formulate a greater portion of the doxycycline in the immediate-release portion for several reasons.

443. First, delayed-release dosage forms are more susceptible to inter-subject and intra-subject variability due to gastrointestinal transit times and pH differences.

444. By placing more of the doxycycline into the immediate release portion, a formulator would reduce the risk of such variability.

445. Second, the ’106/240 applications teach that at least 50% and more preferably 80% of the drug should be released in the upper gastrointestinal tract. *See, e.g.*, ’106 app., 16:12-14.

446. This is consistent with the absorption window of doxycycline known to artisans at the time.

447. Third, because the '106/240 applications express a preference for blood levels between 0.4 and 0.8 μg/ml, this provides additional reason to place more of the doxycycline into the immediate release portion to ensure these blood levels are achieved.

448. One of the ratios that would be obvious to try is 30:10 (IR:DR), specifically for practical reasons.

449. In developing a formulation a person of ordinary skill would select three to four options and then conduct either in vitro, in *silico*, or in vivo testing with each of those options.

450. The obvious choices in this context would be to select ratios that would cover the potential range, which in this case for IR:DR combinations would 30:10 mg (IR:DR) 20:20 (IR:DR), and 10:30 (IR:DR).

451. Second, a skilled artisan would be motivated to select ratios that would be reliably reproducible on the commercial scale.

452. For example, a ratio of 39:1 (IR:DR) would be theoretically possible but would present greater challenges from a manufacturing standpoint to ensure that each dosage form met content uniformity requirements.

453. A skilled artisan would reasonably expect that any of these formulations would achieve blood levels between 0.1 and 1.0 μg/ml.

454. Claim 1 of the '740 patent is directed to a combination of familiar elements, produced according to known methods that yield no more than predictable results.

455. As set forth above, immediate and delayed release doxycycline formulations were commercially available and well-known prior to the priority date of the '740 patent.

456. The absorption properties of doxycycline were also well known, including the absorption properties of doxycycline at low-doses.

457. It was also well known that one way to achieve once-daily dosing of a product would be through a delivery system containing portions with different release profiles.

458. It was also known in the art that doxycycline serum concentrations between 0.1 and 1.0 μg/ml was a desirable therapeutic profile.

459. There were no teachings in the art that would suggest that doxycycline could not be administered once-daily or that IR:DR formulations of doxycycline were unsuitable.

460. The art specifically taught such combinations. Arriving at a suitable ratio of IR to DR portions would require only routine skill and experimentation for a formulator with experience in controlled-release drug delivery.

3. The ’106 Application or the ’240 Application, in View of the ’748 Patent, Renders Obvious Claims 1-8 and 20-21 of the ’532 Patent and Claims 1, 2, 5-15, and 22 of the ’740 Patent

461. Claims 1-8 and 20-21 of the ’532 patent and claims 1-2, 5-15, and 22 of the ’740 patent would have been obvious to one of ordinary skill in the art over the ’106/240 application in view of the ’748 patent.

462. The claims are directed to a combination of familiar elements produced according to known methods that yield no more than predictable results.

(a) Claim 1 of the ’532 Patent and Claim 1 of the ’740 Patent

463. As described above and as set forth below, the ’106 application in combination with the ’748 patent (or the ’240 application in combination with the ’748 patent) discloses, teaches, and suggests pharmaceutical compositions with each of the limitations of claim 1 of each of the patents-in-suit.

(i) An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml,

464. As set forth above, the '106/240 applications expressly discloses oral pharmaceutical compositions of doxycycline that will give steady state blood levels of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml.

465. The '748 patent discloses minocycline, rather than doxycycline, but it discloses an oral pharmaceutical composition that will achieve desired steady-state blood levels after once-daily dosing.

466. The '748 patent is directed to formulations that maintain blood levels in the therapeutic range for up to 24 hours. *See* '748 patent, col. 1:28-37.

467. The '748 patent is directed toward antibiotic levels of minocycline, and reports that it could be used to deliver doses as low as 25 mg, *see id.*, col. 8:11-16.

(ii) the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline (claim 1 of the '740 patent) **/ (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with at least one enteric polymer** (claim 1 of the '532 patent)**;**

468. The '748 patent teaches that desired drug serum levels can be achieved through a once-daily two-pulse delivery systems. '748 patent, col. 3:19-30.

469. The '748 patent also discloses a range of ratios that would be effective to maintain blood levels at the desired therapeutic range. Those ratios range from 51:49 to 80:20. '748 patent, col. 8:16-24; *see also* col. 5:11-21.

470. The ratio limitation of 30:10 (*i.e.* 75:25), which is in claim 1 of each of the patents-in-suit, is within this range disclosed by the '748 patent.

471. In addition, the ’748 patent provides reason to use IR and DR forms of doxycycline with a ratio of IR:DR of greater than 1.

472. Because it was known that doxycycline is absorbed in the upper gastrointestinal tract and has a very long half-life, a skilled artisan would appreciate that the compositions disclosed in the ’748 patent could be successfully modified to achieve the once-daily and sustained-release compositions taught by the ’106/240 applications.

473. One of ordinary skill in the art would also have been motivated to modify the teachings of the ’748 patent to provide a low dose of doxycycline as taught by the ’106/240 applications in order to avoid reduction of healthy flora in the body, the reduction of antibiotic resistant organisms, and the overgrowth of opportunistic yeast and fungi, and to select an amount of IR pellets that is greater than the amount of the DR pellets, including a 40 mg dose containing a 3:1 ratio of IR and DR pellets (*i.e.* containing 30 mg of doxycycline in IR pellets and 10 mg doxycycline in DR pellets).

474. The ’748 patent also discloses techniques for how to modify a twice-daily formulation to achieve once-daily dosing.

475. The ’748 patent discloses the use of coated spheres (*i.e.* pellets), *see* col. 9:58-60, and the use of a combination thereof as described above.

476. In Comparative Example IA, the ’748 patent discloses the administration of 50 mg of immediate release minocycline hydrochloride twice daily to human subjects. *See* ’748 patent, col. 13:21-45.

477. The plasma levels achieved with the immediate release minocycline are then used to compare and evaluate the bioavailability of the once-daily minocycline formulations. *See* ’748 patent, Fig. 5; col. 16:63-18:16.

478. A skilled artisan would have had reason to prepare an oral pharmaceutical composition comprising 40 mg doxycycline with a ratio of IR:DR portions of greater than 1, *e.g.* about 30 mg doxycycline in an IR formulation and about 10 mg doxycycline in a DR portion and would have a reasonable expectation of success in achieving the desired steady state blood levels of doxycycline of a minimum of 0.1 μg/ml. and a maximum of 1.0 μg/ml.

(iii) "and optionally, (iii) one or more pharmaceutically acceptable excipients."

479. The '748 patent disclose several examples of pharmaceutically acceptable excipients. *See* '748 patent, col. 8:65 – col 10:45, col 11:3-26.

480. The '106/240 applications when combined with the '748 patent teach an oral pharmaceutical composition of doxycycline that will give steady-state blood levels of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml, comprising an IR portion with 30 mg and a DR portion with 10 mg along with one or more a pharmaceutically acceptable excipient.

481. The '106/240 applications when combined with the '748 patent render Claim 1 obvious.

(b) Pellet and Dosage Form Limitations (Claims 2, 3 of the '532 Patent; Claims 6-7, and 10 of the '740 Patent)

482. Claim 2 of the '532 patent recites ***"the IR portion is in the form of pellets,"*** claim 7 of the '740 patent recites ***"a dosage form of a combination of pellets."***

483. The '748 patent discloses the use of coated spheres (*i.e.* pellets), *see* col. 9:58-60, and the use of a combination thereof as described above.

484. Claim 3 of the '532 patent recites that ***"the pellets are contained in a capsule."***

485. The ’748 patent teaches that the disclosed uncoated and coated spheres or granules can be filled into capsules, and that such capsules can be administered in a method of treating. *See, e.g.,* ’748 patent, col. 5:22-27.

486. Claim 6 of the ’740 patent recites that the composition is in the form of ***“a granule, tablet, pellet, powder, sachet, capsule, gel, dispersion or suspension”*** and claim 10 recites ***“the DR formulation is in the form of granules, pellets, or tablet.”***

487. The ’748 patent discloses that the DR portion can be in the form of granules or coated spheres (*i.e.* pellets). *See* col. 9:58-60.

488. The ’748 patent discloses that the disclosed compositions could be filled into capsules. *See* ’748 patent, col. 11:66 -12:8.

(c) Process of Preparing Limitations (Claim 20 of the ’532 Patent; Claim 22 of the ’740 Patent)

489. Claim 20 of the ’532 patent and claim 22[2] of the ’740 patent further recite ***“[a] process for preparing an oral pharmaceutical composition”*** and ***“[a] process for preparing a once-daily oral pharmaceutical composition”*** respectively.

490. For the reasons set forth above, the ’748 patent in combination with either the ’572 patent or the ’932 application discloses a composition doxycycline comprising, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml. and a maximum of 1.0 μg/ml., the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients. The ’748 patent also discloses processes for preparing same. *See, e.g.,* ’748 patent, col. 13:47 – col. 15:66.

[2] Claim 22 of the ’740 patent recites “the tetracycline” as the active ingredient instead of “doxycycline.” Because doxycycline is a species within the tetracycline genus, this is not a material difference for purposes of invalidity.

(d) Steady State Limitations
(Claims 4 of the '532 Patent; Claims 2 of the '740 Patent)

491. Claim 4 of the '532 patent and claim 2 of the '740 patent further recites ***"steady state blood levels of the doxycycline of between 0.3 μg/ml to 0.8 μg/ml."***

492. For the reasons set forth above, it would be obvious to modify the formulations disclosed by the '748 patent to achieve the steady-state blood levels of 0.4 to 0.7 μg/ml as taught by the '106/240 applications.

493. When coupled with the disclosure of the '106/240 applications, this combined disclosure renders Claim 4 of the '532 patent and Claim 2 of the '740 patent obvious.

(e) Ratio of IR:DR Limitation
(Claim 5 of the '740 Patent)

494. Claim 5 of the '740 patent recites the further limitation ***"wherein the ratio of IR to DR is 75:25."***

495. For the reasons set forth above with respect to claim 1, the 30:10 (IR:DR) ratio would be obvious in view of the '748 patent in combination with '106/240 applications.

496. In particular, the '748 patent discloses a range of ratios of quick release to coated granules (51:49 – 80:20).

(f) Excipient Limitations
(Claims 5-8, 21 of the '532 Patent; Claims 8, 9, 11-15 of the '740 Patent)

497. Claim 8 of the '740 patent depends from claim 1 and further recites ***"the DR portion comprises at least one enteric polymer."***

498. The '748 patent discloses several pH sensitive enteric polymers that are suitable for use in its DR portion. *See, e.g.*, '748 patent, col. 10:56-11:26.

499. Claim 9 of the '740 patent depends from claim 8 and further recites:

> wherein the enteric polymer is cellulose acetate phthalate; hydroxypropyl methylcellulose phthalate; polyvinyl acetate phthalate; hydroxypropyl methylcellulose acetate succinate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; cellulose acetate succinate; cellulose acetate hexahydrophthalate; cellulose propionate phthalate; a copolymer of methylmethacrylic acid and methyl methacrylate; a copolymer of methyl acrylate, methylmethacrylate and methacrylic acid; a copolymer of methylvinyl ether and maleic anhydride; ethyl methyacrylate -methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer; zein; shellac; poly(methacylic acid-co-ethyl acrylate) 1:1, or combinations thereof.

500. The ’748 patent discloses at least the following enteric polymers: copolymer of methylmethacrylic acid and methyl methacrylate; cellulose acetate phthalate; polyvinyl acetate phthalate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; hydroxypropyl methylcellulose phthalate. *See* ’748 patent, col.11:5-26.

501. When coupled with the disclosure of the ’572 patent (or the ’932 application), this combined disclosure renders Claim 9 obvious.

502. Claim 11 of the ’740 patent depends from claim 1 and further recites ***“one or more pharmaceutically acceptable excipients is incorporated in the IR portion, the DR portion, or both.”***

503. The ’748 patent discloses that both the IR and DR portions contain pharmaceutically acceptable excipients. *See, e.g.,* ’748 patent, col. 4:33 – 5:21.

504. Claim 21 of the ’532 patent and claim 12 of the ’740 patent recites the additional limitation that ***“one or more pharmaceutically acceptable excipients is a binder, a disintegration agent, a filling agent, a surfactant, a solubilizer, a stabilizer, and combinations thereof.”***

505. The ’748 patent discloses a number of well-known binders, disintegration agents, and filing agents, and stabilizers. *See, e.g.,* ’748 patent, col. 8:65-9:18, col. 11:66 – 12:8.

506. Claim 6 of the ’532 patent and claim 13 of the ’740 patent recite the additional limitation that ***“the binder is selected from the group consisting of methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and polyvinylpyrrolidone/vinyl acetate copolymer.”***

507. The ’748 patent discloses the use of several well-known binders, including specifically the following: hydroxyethyl cellulose; polyvinylpyrrolidone; and hydroxypropyl methylcellulose. *See* ’748 patent, col. 8:65 - 9:18.

508. Claim 7 of the ’532 patent and claim 14 of the ’740 patent recite the additional limitation that ***“the disintegration agent is selected from the group consisting of cornstarch, pregelatinized starch, cross-linked carboxymethylcellulose, sodium starch glycolate, and cross-linked polyvinylpyrrolidone.”***

509. The ’748 patent discloses the use of well-known disintegration agents, including starch and pregelatinzed starch. *See, e.g.,*’748 patent, col. 8:5 – 9:18.

510. Claim 8 of the ’532 patent and claim 15 of the ’740 patent recite the additional limitation that ***“the filling agents are selected from the group consisting of lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, and polyethylene glycol.”***

511. The ’748 patent discloses the use of well-known filing agents, including lactose and microcrystalline cellulose. *See, e.g.,* ’748 patent, col. 8:65 – 9:18.

4. The ’106 Application or the ’240 Application, in View of the ’572 Patent or the ’932 Application, Render Obvious All Asserted Claims of the Patents-in-Suit

512. For the reasons discussed above, claims 1-8 and 15-21 of the ’532 patent and claims 1-2, 5-15, and 19-22 of the ’740 patent would have been obvious to one of ordinary skill in the art over the ’106/240 applications in view of the ’572 or the ’932 application.

513. There is an express suggestion in the art to combine the ’106/240 applications with the ’572 patent or the ’932 application, given that the ’572 patent and the ’932 application expressly incorporates by reference the ‘854 application, which is the non-provisional priority document to which the ’106/240 applications claim priority.

514. Also, each of these references are directed to doxycycline compositions and have the same assignee and named inventor.

515. A skilled artisan, therefore, would be motivated to combine the ’106/240 applications with either the ’572 patent or the ’932 application.

516. By combining these references, a skilled artisan would appreciate that to achieve steady-state blood levels between 0.1 and 1.0 μg/ml, he should select a 40 mg dose.

517. Although a skilled artisan could have readily deduced the correct dosage amount from the ’106/240 applications alone, the ’572 patent or the ’932 application confirm that dosage amount.

518. Based on this information, a skilled artisan could then determine through routine testing and optimization what ratios would achieve the desired blood levels of 0.1 to 1.0 in accordance with the teachings of the ’106/240 applications.

519. A skilled artisan would also look to the ’572 patent or the ’932 application for therapeutic applications of low doses of doxycycline.

520. Because each of these references relates to doses of doxycycline that achieve blood levels between 0.1 and 1.0 μg/ml, a skilled artisan would immediately recognize that the compositions disclosed by the ’106/240 applications could be used in accordance with the methods claimed by the ’572 patent or the ’932 application.

(a) Method of Treating Limitations (Claims 15, 16 of the '532 Patent; Claims 19, 20 of the '740 Patent)

521. Claim 15 of the '532 patent and claim 19 of the '740 patent further recite ***"[a] method for treating rosacea in a mammal in need thereof, comprising administering an oral pharmaceutical composition."***

522. Claim 15 of the '532 patent and claim 19 of the '740 patent merely adds the limitation of "a method treating rosacea in a mammal thereof" to the limitations already recited in claim 1 of their respective patents, which, for the reasons stated above, are disclosed by the '106/240 applications.

523. The '106/240 applications further teach the treatment of inflammatory skin diseases and acne (*e.g.* rosacea) by the once daily administration (*see, e.g.*, '106 app., 3:6-24) of a tetracycline compound (*see, e.g.*, 4:15-21) and that doxycycline is one such tetracycline compound.

524. The '572 patent (col. 4:25-45) or the '932 application (at 6:34 -7:4) teaches the treatment of rosacea with low doses of doxycycline.

525. Claim 16 of the '532 patent and claim 20 of the '740 patent further recites ***"wherein the mammal is a human."***

526. The '106/240 applications (*see, e.g.* 7:12-14) and the '572 patent (*see e.g.*, col. 3:45-46) or the '932 application (*see, e.g.*, 5:17-21) teach administration to a human.

(b) Pellet and Dosage Form Limitations (Claim 17 of the '532 Patent)

527. Claims 3 and 17 of the '532 patent recites that ***"the pellets are contained in a capsule,"*** with claim 17 reciting the added limitation of a method of treating.

528. The ’106/240 applications disclose that the doxycycline composition can be in the form of beadlets with different coatings and release profiles and that such beadlets may be filled in a capsule.

529. For the reasons discussed with respect to claim 15 of the ’532 patent and claim 19 of the ’740 patent, the “method of treatment” limitation of claim 17 is not patentable difference.

(c) Steady State Limitations (Claim 18 of the ’532 Patent; Claim 21 of the ’740 Patent)

530. Claim 4 of the ’532 patent and claim 2 of the ’740 patent further recites ***“steady state blood levels of the doxycycline of between 0.3 µg/ml to 0.8 µg/ml”*** and claim 18 of the ’532 patent and claim 21 of the ’740 patent correspondingly recite a ***method of treating rosacea with a composition achieving that steady state blood level***.

531. The ’106/240 applications teach that the composition will give blood levels of the doxycycline of between 0.4 µg/ml to 0.8 µg/ml. *See, e.g., id.,13:20*-24.

532. For the reasons discussed above with respect to claim 4 and 15 of the ’532 patent, the ’106/240 applications combined with the ’572 patent (or the ’932 application) render claim 18 and 21 obvious.

D. The Asserted Claims of the Patents-in-Suit are Invalid in View of Periostat®

1. Periostat® in View of the ’748 Patent Renders Obvious Claims 1-8 and 20-22 of the ’532 Patent and Claims 1, 2, 5-15 and 22 of the ’740 Patent

533. Claims 1-8 and 20-22 of the ’532 patent and claims 1-2, 5-15 and 22 of the ’740 patent would have been obvious to one of ordinary skill in the art over Periostat® in view of the ’748 patent.

534. As described above, Periostat® is a 20 mg doxycycline immediate release formulation that was commercially available as of 1998.

535. The prescribing information for Periostat® indicates that it is labeled for twice-daily dosing. *See* http://www.accessdata.fda.gov/ drugsatfda_docs/label/1998/50744lbl.pdf (Periostat® Approved Labeling, Dated September 30, 1998).

536. The pharmacokinetic properties of Periostat® both after single dosing and after steady-state dosing would have been readily ascertainable by a person of skill in the art, either by reviewing the Periostat® Approval Package or through routine pharmacokinetic testing.

537. There existed both a design need and commercial market pressures to develop a once-daily formulation for Periostat®.

538. The development of once-daily formulations is a common commercial strategy that had been generally employed for years before the priority date of the patents-in-suit.

539. A formulator would know that the textbook benefits of once-daily formulation included, among other things, (1) improved patient compliance and (2) improved efficacy with less fluctuation of drug levels.

540. CollaGenex reported in its publicly-available 2001 Annual Report to shareholders that it was developing a once daily formulation of Periostat® (p. 12).

541. This confirms that a skilled artisan would be aware of the desirability of and market for such a formulation for Periostat®.

542. A formulator faced with the task of modifying Periostat® to become a once-daily formulation would begin by reviewing publicly-available information about Periostat®, including the Periostat® Approval Package (AMORA_00256847-00257171).

543. From that information, a skilled artisan would know the following:

- the formulation should not exceed the steady-state threshold level of 1.0 μg/ml. of doxycycline (AMORA_0256948; AMORA_00257036; AMORA_0257013);
- that doxycycline has a half life between 14.5-22 hours (AMORA_00256974);

- a 20 mg IR formulation administered once-daily would achieve a maximum steady-state blood level of 0.489 μg/ml of doxycycline (AMORA_0027027-7036);
- a doxycycline formulation with at least 20 mg IR administered once-daily would be expected to have steady state have a minimum blood level above 0.1 μg/ml. (AMORA_0027027-7036);
- a 20 mg IR formulation administered twice-daily (total daily dose of 40 mg) would achieve a maximum steady-state blood level of between 0.746 μg/ml. to about 0.772 μg/ml. of doxycycline (AMORA_0027027-7036; AMORA_00257036-7040); and
- a 40 mg IR formulation administered once-daily would achieve a maximum steady-state blood of 0.834 of doxycycline (AMORA_00257036-7040).

544. Even if this pharmacokinetic information was not available, these properties are intrinsic to Periostat® and would have been readily ascertainable by a skilled artisan through routine testing.

545. In light of the long half-life associated with doxycycline and the knowledge that 40 mg of doxycycline administered in IR form once-daily would on average remain below the steady-state threshold of 1.0 μg/ml, there would be a finite number of options for developing a once-daily formulation that would be readily considered by a skilled artisan and a skilled artisan would have a reasonable expectation of success with any of these options.

546. A skilled artisan would recognize that one option for a once-daily Periostat® formulation would be to administer 40 mg of doxycycline in an immediate-release dosage form.

547. Based on the known pharmacokinetics of Periostat®, a skilled artisan would have had at least a reasonable expectation of success that a 40 mg IR doxycycline formulation would achieve blood levels below the 1.0 μg/ml threshold.

548. Another option that a skilled artisan would consider would be to administer 40 mg of doxycycline using a modified-release approach.

549. The three principle alternatives to an immediate release dosage form would be a delayed-release mechanism, a sustained release mechanism, or a combination of immediate release, delayed-release and/or sustained-release mechanisms.

550. A skilled artisan would recognize that a sustained release mechanism is unnecessary for doxycycline because of its long-half and also because it was generally known at the time that doxycycline is primarily absorbed from the upper gastrointestinal tract.

551. Thus, as an alternative to an IR approach, a skilled artisan would be motivated to select either a DR release approach or a combination of IR and DR.

552. These textbook approaches to once-daily dosing were well known in the art prior to November 2002, when the alleged invention occurred.

553. Dr. Chang, the first named inventor of the ’740 patent, himself described these techniques in a 1990 textbook that would have been readily available to formulators.

554. Dr. Chang described the purpose of his book chapter as “to provide sufficient experimental detail to allow the novice formulator to initiate preparation of a prolonged-action dosage form.” Chang and Robinson, at 242; *see also id.* at 200.

555. A skilled artisan would expect a delayed-release formulation to be a viable option because there was at least one commercial delayed-release formulation on the market (Doryx®).

556. It was known in the art that doxycycline administered through a delayed-release formulation can have, on average, the same rate and extent of absorption as doxycycline administered in immediate release form. *See* Williams et al., at 104.

557. Thus, a skilled artisan would reasonably expect that 40 mg of doxycycline, formulated as a delayed-release only formulation, would also achieve steady-state blood levels between 0.1 and 1.0 μg/ml.

558. A third option a formulator would immediately recognize is that he could administer 40 mg of doxycycline in a combination of IR and DR forms and also achieve steady-state blood levels between 0.1 and 1.0 μg/ml.

559. So long as at least 20 mg of doxycycline is administered in immediate release form, a skilled artisan would expect that the formulation would achieve steady-state blood levels between 0.1 and 1.0 μg/ml.

560. Selecting the precise ratio of IR to DR would be simply a question of routine optimization and experimentation that are well within the ability of a skilled artisan. DTX 35.

561. Dr. Bergstrom conducted *in silico* modeling with various ratios of IR and DR potions.

562. Every 40 mg formulation that Dr. Bergstrom modeled, including 100% IR and 100% DR, shows that they are capable of achieving steady-state blood levels of a minimum of 0.1 μg/ml to a maximum of 1.0 μg/ml.

563. Dr. Bergstrom's experiments, including 100% IR and 100% DR, show that they are capable of achieving steady-state blood levels of a minimum of 0.1 μg/ml to a maximum of 1.0 μg/ml.

564. Dr. Bergstrom's experiments confirm that the 30:10 ratio is not critical to achieving the claimed steady-state blood levels.

565. Thus, the 30:10 ratio is not critical to achieving such blood levels.

566. A skilled artisan would be motivated to formulate a greater portion of the doxycycline in the immediate-release portion for several reasons.

567. First, it was known in the art that doxycycline is primarily absorbed in the upper gastrointestinal tract and that doxycycline has a long half-life.

568. This factor would lead a skilled artisan to select an immediate release portion to deliver the majority of the doxycycline.

569. Second, delayed-release dosage forms are more susceptible to inter-subject and intra-subject variability due to gastrointestinal transit times and pH differences.

570. By placing more of the doxycycline into the immediate release portion, a formulator would reduce the risk of such variability.

571. Third, a skilled artisan would also select a higher portion to be formulated into the IR portion because of manufacturing and cost considerations.

572. One of the ratios that would be obvious to try is 30:10 (IR:DR).

573. In developing a formulation a person of ordinary skill would select three to four options and then conduct either *in vitro*, *in silico*, or *in vivo* testing with each of those options.

574. The obvious choices in this context would be to select ratios that would cover the range of potential ratios.

575. In this case, the obvious options for IR:DR combinations would 30:10 mg (IR:DR), 20:20 (IR:DR), and 10:30 (IR:DR).

576. Second, a skilled artisan would be motivated to select ratios that would be reliably reproducible on the commercial scale.

577. A ratio of 39:1 (IR:DR) would be theoretically possible but would present greater challenges from a manufacturing standpoint to ensure that each dosage form met content uniformity requirements.

578. A skilled artisan would reasonably expect that any of these formulations would achieve blood levels between 0.1 and 1.0 μg/ml.

579. General knowledge and skill would lead a formulator to try a formulation within the scope of Claim 1 to achieve a once-daily version of Periostat® as described above.

580. A skilled artisan could also look to examples of other once-daily tetracycline delivery systems.

581. The closest tetracycline to doxycycline is minocycline, which the art recognized as sharing similar physiochemical and absorption characteristics.

582. Thus, a skilled artisan would consider once-daily minocycline delivery systems as potential solutions for formulating a once-daily doxycycline product.

583. The ’748 patent is an example of one such system.

584. The ’748 patent discloses and teaches once-daily delivery systems for minocycline, which is a second-generation tetracycline that has similar properties to doxycycline.

585. The ’748 patent explains that its object is “a once-a-day delivery system which maintains therapeutic blood level concentrations of the medicament in a patient for twenty-four hours.” ’748 patent, col. 1:12-15.

586. The ’748 patent discloses formulations that include a pulsed-release formulation comprised of a major portion of a first pulse of quick release granules and a minor portion of a second pulse of coated granules. *Id.* at col. 1, 17-22.

587. The ’748 patent discloses that improved bioavailability can be achieved by “increasing the ratio of quick release initial loading pellets to slow release secondary loading coated pellets and by using a modified coating composition for the latter.” *Id.*, col. 3:48-52.

588. The “secondary loading pellets” disclosed in the ’748 patent are coated with a pH-sensitive coating, *id.*, col. 3:55-58—*i.e.* an enteric polymer.

(a) Claim 1 of the ’532 Patent and Claim 1 of the ’740 Patent

589. As described above and as set forth below, Periostat® in combination with the ’748 patent discloses, teaches, and suggests each of the limitations of claim 1 of each of the patents-in-suit.

(i) An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml,

590. As set forth above, a skilled artisan seeking to formulate a once-daily version of Periostat® would understand that steady state blood levels should remain below a maximum of 1.0 µg/ml.

591. A skilled artisan would predict that so long as 20 mg of doxycycline is administered once-daily that it will result in steady-state blood levels of at least about 0.1 µg/ml.

592. Although the ’748 patent is preferably directed toward antibiotic levels of minocycline, it also reports that it could be used to deliver doses as low as 25 mg. ’748 patent, col. 8:11-16.

(ii) the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline (claim 1 of the ’740 patent) / (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with at least one enteric polymer (claim 1 of the ’532 patent);

593. The ’748 patent teaches that desired drug serum levels can be achieved through a once-daily two-pulse delivery systems. ’748 patent, col. 3:19-30.

594. The first pulse is delivered through quick release (*i.e.* IR) granules and the second pulse is delivered through coated granules that provide a delayed release.

595. The ’748 patent discloses that improved bioavailability can be achieved by “increasing the ratio of quick release initial loading pellets to slow release secondary loading coated pellets and by using a modified coating composition for the latter.” *Id.*, col. 3:48-52.

596. The “secondary loading pellets” are coated with a pH-sensitive coating, *id.*, col. 3:55-58—*i.e.* an enteric polymer. Accordingly, the ’748 patent expressly discloses dosage forms with IR and DR portions as claimed by the ’740 patent.

597. The ’748 patent also discloses a range of ratios that would be effective to maintain blood levels at the desired therapeutic range. Those ratios range from 51:49 to 80:20. ’748 patent, col. 8:16-24; *see also* col. 5:11-21.

598. Claim 1 of the ’740 patent’s ratio of 30:10 (*i.e.* 75:25) is within this range disclosed by the ’748 patent.

599. The ’748 patent provides reason to use IR and DR forms of doxycycline with a ratio of IR:DR of greater than 1.

600. The ’748 patent teaches that bioavailability can be improved by increasing the ratio of IR pellets to DR pellets.

601. One of ordinary skill in the art would also have had a reason and would have been motivated to increase the relative amount of IR to DR portions of doxycycline, in view of the known similarities of the two tetracycylines, and the preferential absorption of both minocycline and doxycycline in the upper GI tract.

602. A skilled artisan would view the pharmacokinetics of minocycline and doxycycline as comparable and as overlapping to a considerable extent.

603. Thus, a skilled artisan would have reason and motivation to substitute doxycycline for minocycline in the composition described in the ’748 patent.

604. Because it was known that doxycycline is absorbed in the upper gastrointestinal tract and has a very long half life, a skilled artisan would appreciate that the compositions disclosed in the ’748 patent could be successfully modified to achieve a once-daily formulation of Periostat®.

605. One of ordinary skill in the art would also have been motivated to modify the teachings of the ’748 patent to provide a low dose of doxycycline as exemplified by Periostat® and its known uses, and to select an amount of IR pellets that is greater than the amount of the DR pellets, including a 40 mg dose containing a 3:1 ratio of IR and DR pellets (*i.e.* containing 30 mg of minocycline in IR pellets and 10 mg minocycline in DR pellets).

606. One of ordinary skill in the art would have had a reason to include a IR:DR ratio of greater than 1 in view of the long half-life of doxycycline (reported to be 18 hours for once daily dosing of Periostat® according to the Periostat® insert).

607. It was known that doxycycline is absorbed preferentially in the upper gastrointestinal tract, and that it has a very long half-life which provides for once daily administration.

608. Thus, a skilled artisan would have had reason to provide a greater ratio of IR to DR portions to ensure that most of the doxycycline will be released immediately and absorbed with an expectation that the blood levels of doxycycline will remain high enough for activity over a period of about 24 hours.

609. The ’748 patent also discloses techniques for how to modify a twice-daily formulation to achieve once-daily dosing.

610. In Comparative Example IA, the '748 patent discloses the administration of 50 mg of immediate release minocycline hydrochloride twice daily to human subjects. *See* '748 patent, col. 13:21-45.

611. The plasma levels achieved with the immediate release minocycline are then used to compare and evaluate the bioavailability of the once-daily minocycline formulations. *See* '748 patent, Fig. 5; col. 16:63-18:16.

612. A skilled artisan would have had reason to prepare an oral pharmaceutical composition comprising 40 mg doxycycline with a ratio of IR:DR portions of greater than 1, *e.g.*, about 30 mg doxycycline in an IR formulation and about 10 mg doxycycline in a DR portion and would have a reasonable expectation of success in achieving the desired steady state blood levels of doxycycline of a minimum of 0.1 μg/ml. and a maximum of 1.0 μg/ml.

(iii) "and optionally, (iii) one or more pharmaceutically acceptable excipients."

613. The '748 patent discloses several examples of pharmaceutically acceptable excipients. *See* '748 patent, col. 8:65 – col 10:45, col 11:3-26.

614. Arriving at a suitable ratio of IR to DR portions would require only routine skill and experimentation for a formulator with experience in controlled-release drug delivery in view of Periostat® and the '748 patent.

(b) Process of Preparing Limitations Claims (Claim 20 of the '532 Patent; Claim 22 of the '740 Patent)

615. Claim 20 of the '532 patent and claim 22[3] of the '740 patent further recite ***"[a] process for preparing an oral pharmaceutical composition"*** and ***"[a] process for preparing a once-daily oral pharmaceutical composition"*** respectively.

616. For the reasons set forth above, Periostat® in combination with the '748 patent renders obvious a composition doxycycline comprising, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml. and a maximum of 1.0 μg/ml, the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients. The '748 patent also discloses processes for preparing same. *See, e.g.*, '748 patent, col. 13:47 – col. 15:66.

617. When coupled with Periostat®, this combined disclosure renders Claim 22 obvious.

(c) Pellet and Dosage Form Dependent Claim Limitations (Claims 2-3 of the '532 Patent; Claims 6-7, and 10 of the '740 Patent)

618. Claim 2 of the '532 patent recites ***"the IR portion is in the form of pellets,"*** claim 7 of the '740 patent recites ***"a dosage form of a combination of pellets."***

619. The '748 patent discloses the use of coated spheres (*i.e.* pellets), *see* col. 9:58-60, and the use of a combination thereof as described above.

620. Claim 3 of the '532 patent recites that ***"the pellets are contained in a capsule."***

[3] Claim 22 of the '740 patent recites "the tetracycline" as the active ingredient instead of "doxycycline." Because doxycycline is a species within the tetracycline genus, this is not a material difference for purposes of invalidity.

621. The ’748 patent teaches that the disclosed uncoated and coated spheres or granules can be filled into capsules, and that such capsules can be administered in a method of treating. *See, e.g.,* ’748 patent, col. 5:22-27.

622. Claim 6 of the ’740 patent recites that the composition is in the form of ***“a granule, tablet, pellet, powder, sachet, capsule, gel, dispersion or suspension”*** and claim 10 recites ***“the DR formulation is in the form of granules, pellets, or tablet.”***

623. The ’748 patent discloses that the DR portion can be in the form of granules or coated spheres (*i.e.* pellets). *See* col. 9:58-60.

624. The ’748 patent discloses that the disclosed compositions could be filled into capsules. *See* ’748 patent, col. 11:66 -12:8.

(d) Steady State Dependent Claim Limitations (Claims 4 of the ’532 Patent; Claims 2 of the ’740 Patent)

625. Claim 4 of the ’532 patent and claim 2 of the ’740 patent further recites ***“steady state blood levels of the doxycycline of between 0.3 μg/ml to 0.8 μg/ml.”***

626. Plaintiffs contend that this language does not recite a minimum or a maximum level of doxycycline and that, as long as a blood level between 0.3 and 0.8 μg/ml is achieved during steady-state dosing by a subject, that this limitation is met.

627. Under such a construction, any 40 mg formulation that would achieve steady-state blood levels between 0.1 and 1.0 μg/ml would also be expected to achieve a blood level between 0.3 and 0.8 μg/ml in at least some people some of the time. *See, e.g.*, Periostat® Approval Package, at AMORA_00257033.

628. Claim 2 is also obvious in light of Periostat® in combination with the ’748 patent.

(e) Ratio of IR:DR Dependent Claim Limitation (Claim 5 of the '740 Patent)

629. Claim 5 of the '740 patent recites the further limitation ***"wherein the ratio of IR to DR is 75:25."***

630. For the reasons set forth above with respect to Claim1, the 30:10 (IR:DR) ratio would be obvious in view of the '748 patent in combination with '106/240 applications. In particular, the'748 patent discloses a range of ratios of quick release to coated granules (51:49 – 80:20).

631. When coupled with Periostat®, Claim 5 would be obvious.

(f) Excipient Dependent Claim Limitations (Claims 5-8, 21 of the '532 Patent; Claims 8, 9, 11-15 of the '740 Patent)

632. Claim 8 of the '740 patent depends from claim 1 and further recites ***"the DR portion comprises at least one enteric polymer."***

633. The '748 patent discloses several pH sensitive enteric polymers that are suitable for use in its DR portion. *See, e.g.,* '748 patent, col. 10:56-11:26.

634. Claim 9 of the '740 patent depends from claim 8 and further recites:

> wherein the enteric polymer is cellulose acetate phthalate; hydroxypropyl methylcellulose phthalate; polyvinyl acetate phthalate; hydroxypropyl methylcellulose acetate succinate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; cellulose acetate succinate; cellulose acetate hexahydrophthalate; cellulose propionate phthalate; a copolymer of methylmethacrylic acid and methyl methacrylate; a copolymer of methyl acrylate, methylmethacrylate and methacrylic acid; a copolymer of methylvinyl ether and maleic anhydride; ethyl methyacrylate -methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer; zein; shellac; poly(methacylic acid-co-ethyl acrylate) 1:1, or combinations thereof.

635. The '748 patent discloses at least the following enteric polymers: copolymer of methylmethacrylic acid and methyl methacrylate; cellulose acetate phthalate; polyvinyl acetate

phthalate; cellulose acetate trimellitate; hydroxypropyl methylcellulose succinate; hydroxypropyl methylcellulose phthalate. *See* '748 patent, col.11:5-26.

636. When coupled with Periostat®, this combined disclosure renders Claim 9 obvious.

637. Claim 11 of the '740 patent depends from claim 1 and further recites ***"one or more pharmaceutically acceptable excipients is incorporated in the IR portion, the DR portion, or both."***

638. The '748 patent discloses that both the IR and DR portions contain pharmaceutically acceptable excipients. *See, e.g.,* '748 patent, col. 4:33 – 5:21.

639. When coupled with Periostat®, this combined disclosure renders Claim 11 obvious.

640. Claim 21 of the '532 patent and claim 12 of the '740 patent recite the additional limitation that ***"one or more pharmaceutically acceptable excipients is a binder, a disintegration agent, a filling agent, a surfactant, a solubilizer, a stabilizer, and combinations thereof."***

641. The '748 patent discloses a number of well-known binders, disintegration agents, and filing agents, and stabilizers. *See, e.g.,* '748 patent, col. 8:65-9:18, col. 11:66 – 12:8.

642. When coupled with Periostat®, this combined disclosure renders Claim 12 obvious.

643. Claim 6 of the '532 patent and claim 13 of the '740 patent recite the additional limitation that ***"the binder is selected from the group consisting of methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and polyvinylpyrrolidone/vinyl acetate copolymer."***

644. The ’748 patent discloses the use of several well-known binders, including specifically the following: hydroxyethyl cellulose; polyvinylpyrrolidone; and hydroxypropyl methylcellulose. *See* ’748 patent, col. 8:65 - 9:18.

645. Claim 7 of the ’532 patent and claim 14 of the ’740 patent recite the additional limitation that ***“the disintegration agent is selected from the group consisting of cornstarch, pregelatinized starch, cross-linked carboxymethylcellulose, sodium starch glycolate, and cross-linked polyvinylpyrrolidone.”***

646. The ’748 patent discloses the use of well-known disintegration agents, including starch and pregelatinzed starch. *See, e.g.,*’748 patent, col. 8:5 – 9:18.

647. When ***coupled*** with Periostat®, this combined disclosure renders Claim 13 obvious.

648. Claim 8 of the ’532 patent and claim 15 of the ’740 patent recite the additional limitation that ***“the filling agents are selected from the group consisting of lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, and polyethylene glycol.”***

649. The ’748 patent discloses the use of well-known filing agents, including lactose and microcrystalline cellulose. *See, e.g.,* ’748 patent, col. 8:65 – 9:18.

650. When coupled with ***Periostat***®, this combined disclosure renders Claim 15 obvious.

2. Periostat® in View of the ’748 Patent and the 2001 Annual Report, Renders Obvious Claims 15-19 of the ’532 Patent and Claims 19-21 of the ’740 Patent

651. Claims 15-19 of the ’532 patent and claims 19-21 of the ’740 patent would be obvious in light of Periostat® and the ’748 patent in view of the CollaGenex 2001 Annual Report.

652. The 2001 Annual Report teaches that Periostat® may be useful in treating rosacea.

653. The 2001 Annual Report discloses that Periostat® had shown efficacy in treating inflammatory acne.

654. Specifically, the 2001 Annual Report, at 3, states:

> In particular, we received a number of anecdotal reports that patients on Periostat were experiencing significant improvements in their acne conditions. To confirm these reports, during 2001 we conducted a 59-patient, double-blind, placebo controlled clinical trial to evaluate the efficacy of Periostat in the treatment of acne. On October 1, 2001 we announced the statistically and clinically significant results: the patients on Periostat experienced a reduction of over 50% in the number of both inflammatory lesions and comedones.

655. The 2001 Annual Report also provided commercial reasons to pursue a rosacea treatment, stating: "In 2000, dermatologists wrote 7.8 million prescriptions, valued at $1.25 billion, for drugs to treat acne and rosacea." *Id.*

656. The 2001 Annual Report further indicates that CollaGenex believed Periostat® may be effective for treating rosacea. *Id.* at 13 ("We are currently in discussions with the FDA regarding protocols for additional trials with Periostat for acne and rosacea.").

657. In light of the 2001 Annual Report, a skilled artisan would be motivated to try to use Periostat® or a once-daily version of Periostat® to treat rosacea and other inflammatory skin conditions.

(a) Method of Treating Claims (Claims 15, 16 of the '532 Patent; Claims 19, 20 of the '740 Patent)

658. Claim 15 of the '532 patent and claim 19 of the '740 patent further recite ***"[a] method for treating rosacea in a mammal in need thereof, comprising administering an oral pharmaceutical composition."***

659. Claim 15 of the ’532 patent and claim 19 of the ’740 patent merely adds the limitation of “a method treating rosacea in a mammal thereof” to the limitations already recited in claim 1 of their respective patents, which, for the reasons stated above, are disclosed by the ’106/240 applications.

660. The oral pharmaceutical composition recited in Claim 19 has the same limitations as the oral pharmaceutical composition of Claim 1. For the reasons set forth above as to why it would be obvious to formulate a once-daily version of Periostat®, it would also be obvious to try to treat rosacea with a once-daily version of Periostat® in view of the disclosure found in the 2001 Annual Report.

661. Claim 16 of the ’532 patent and claim 20 of the ’740 patent further recites ***“wherein the mammal is a human.”***

662. As Periostat® is administered to humans it would also be obvious to use the method disclosed above to treat a human.

663. For the reasons set forth above as to why it would be obvious to formulate a once-daily version of Periostat®, it would also be obvious to try to treat rosacea in humans with a once-daily version of Periostat® in view of the disclosure found in the 2001 Annual Report.

(b) Pellet and Dosage Form Dependent Claim Limitations (Claim 17 of the ’532 Patent)

664. Claims 3 and 17 of the ’532 patent recite that ***“the pellets are contained in a capsule,”*** with claim 17 reciting the added limitation of a method of treating.

665. For the reasons set forth above with respect to claims 2 and 15, Periostat®, the ’748 patent, and the 2001 Annual Report combined render claim 17 obvious.

(c) Steady State Dependent Claim Limitations (Claim 18 of the '532 Patent; Claim 21 of the '740 Patent)

666. Claim 4 of the '532 patent and claim 2 of the '740 patent further recite ***"steady state blood levels of the doxycycline of between 0.3 µg/ml to 0.8 µg/ml"*** and claim 18 of the '532 patent and claim 21 of the '740 patent correspondingly recite a ***method of treating rosacea with a composition achieving that steady state blood level***.

667. For the reasons set forth above with respect to Claims 19 and Claim 2, it would have been obvious to administer the disclosed composition to achieve the blood levels recited by Claim 21.

(d) There are no secondary considerations that support a conclusion of nonobviousness.

(i) Failure of Others

668. The doxycycline formulations developed by F.H. Faulding & Co. Limited ("Faulding") do not constitute a failure of others because there is no evidence that each of those formulations would not be therapeutically effective.

669. To the contrary, the evidence shows that at least one of those formulations would achieve steady-state blood levels within the range claimed by Chang and taught by the prior art.

670. The doxycycline formulations developed by Faulding also do not constitute a failure of others because the reason CollaGenex decided not to pursue further development was for business and commercial reasons rather than due to technical or scientific reasons.

671. The work by F.H. Faulding does not constitute a failure of others because F.H. Faulding and Shire Laboratories were both working at the direction of CollaGenex.

(ii) Copying

672. There is no evidence of record to suggest that the asserted claims are nonobvious because of any alleged copying.

673. To the extent an ANDA applicant's dosage form is similar to Oracea®, such similarities are due to FDA regulatory requirements as opposed to any percieved technical advantages of the Oracea® formulation.

(iii) Unexpected Results

674. There is no evidence of record to suggest that the asserted claims are nonobvious because of any alleged unexpected results.

675. There are no unexpected differences between the results obtained by the subject-matter claimed by the patents-in-suit and the closest prior art.

676. It is not unexpected that a therapeutic, controlled release, once-daily formulation of doxycycline that provided steady-state plasma concentrations of a minimum of 0.1 μg/ml. and a maximum of 1.0 μg/ml could have been formulated.

677. It is not unexpected that a 40 mg dose of doxycycline would provide steady-state plasma concentrations of a minimum of 0.1 μg/ml. and a maximum of 1.0 μg/ml.

678. There is also nothing unexpected or surprising that a 40 mg doxycycline formulation could be used to treat rosacea.

(iv) Acceptance in the Industry

679. There is no evidence to suggest that the asserted claims are nonobvious due to any alleged acceptance or praise in the industry.

(v) Commercial Success

680. There is no evidence to suggest any commercial success of Oracea® is due to the patentable features of the asserted claims of the Chang patents.

681. To the extent that Oracea® is commercially successful, its sales are attributable to Galderma's marketing efforts or features of Oracea® that existed in the prior art, and not any allegedly novel features claimed in the patents-in-suit.

682. Absent Galderma's significant expenditures in marketing, promotional, and sales for Oracea, Oracea's sales would have been significantly less.

683. Even though studies showed Periostat® to be effective at treating rosacea, CollaGenex did not seek FDA approval to market Periostat® for that indication.

684. There are no material clinical or therapeutic differences between Periostat® and Oracea®.

685. Any commercial success of Oracea is also because it was marketed, and approved by the FDA, for the treatment of acne/rosacea, not because it was nonobvious.

686. Galderma's business focus is on smaller market niches, with much of its focus being on marketing and promotion, rather than fundamental R&D.

687. Oracea's sales have been significantly based on a large and systematic marketing, promotion and direct sales campaign, including: (a) direct-to-consumer advertising aimed at expanding the rosacea market; (b) payments to pharmacy benefit managers to improve the formulary position of Oracea; (c) rebate coupons to consumers to lower the maximum copayment; and (d) "detailing" to doctors in order to expand the prescriber base beyond the limited number of dermatologists responsible for most Oracea prescriptions.

688. Physicians do not perceive Oracea's benefits over alternative rosacea therapies are great enough to justify prescribing it unless significant economic incentives, such as rebates, are given to consumers to defray their copayments. DTX 1201 at GAL 0220957; DTX 1192 at GAL 0222629.

(vi) Teaching Away

689. There is no evidence to suggest that the asserted claims are nonobvious due to any alleged teaching away of the claimed inventions in the pertinent prior art.

690. The pertinent prior art does not criticize, discredit, or otherwise discourage investigation into the invention claimed, even though it may disclose other approaches for delivering tetracyclines.

691. The prior art does not teach away from once-daily administration of 40 mg of doxycycline to achieve steady-state blood levels between 0.1 and 1.0 μg/ml., rather it expressly embraces it.

692. The prior art also does not teach away from using IR and DR components to achieve such a release profile, rather it specifically identifies that as one formulation approach that would be suitable.

(vii) Long-Felt, but Unmet Need

693. There is no evidence to suggest that the asserted claims are nonobvious due to any alleged long-felt, but unmet need.

694. Oracea has not and did not fulfill a long-felt need to provide an effective oral treatment for rosacea.

695. At the time that the patents-in-suit were filed, there was not a long-felt need for a modified-release formulation to provided once-daily doxycycline dosing because doxycycline is inherently a once-daily treatment.

696. There was also not a long-felt need for a new orally-administered treatment for rosacea as Periostat® was shown to be effective for treating rosacea and it was commercially available well before the filing of the Chang patents, as were other doxycycline products.

IV. EQUITABLE DEFENSES—INEQUITABLE CONDUCT, BREACH OF CONTRACT, AND UNCLEAN HANDS

A. The '532 and '740 Patents are Unenforceable Due to Plaintiffs' Inequitable Conduct

697. REDACTED at Supernus's predecessor-in-interest, Shire Laboratories, Inc. ("Shire").

698. On April 7, 2004, Shire, REDACTED filed Application No. 10/819,620 ("the '620 application").

699. The '620 application issued as the '532 patent.

700. On April 7, 2003, Shire, REDACTED filed Provisional Application No. 60/460,963 ("the '963 provisional application").

701. On February 26, 2004, Shire, REDACTED filed Provisional Application 60/547,964 ("the '964 provisional application").

702. REDACTED

703. REDACTED that issued as the '532 patent, and upon which the '740 patent claims priority.

704. REDACTED the two provisional applications to which the '532 and '740 patents purport to claim priority—the '963 provisional application and the '964 provisional application.

705. REDAC participated in at least some aspects of the preparation of the '963 provisional, the '964 provisional, and the '620 applications.

706. The phrase "give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml" appears in independent claims 1, 15 and 20 of the '532 patent.

707. The ’963 provisional application as filed describes certain simulated blood level profiles determined by *in silico* modeling that, in turn, relied in part upon certain data from human clinical trials.

708. The ’964 provisional application as filed contained certain information regarding a clinical study comparing certain pharmacokinetic properties of a once-daily oral dose of a 30 mg IR, 10 mg DR doxycycline capsule formulation developed by Shire versus a twice-daily oral dose of Periostat® (doxycycline hyclate tablets), 20 mg.

709. During prosecution, REDACTED

710. But REDAC intentionally—and with deceptive intent— REDACTED

711. All claims of the patents-in-suit require a pharmaceutical composition that “give[s] ***steady state*** blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml.”

712. REDACTED the ’963 provisional application without the benefit of any *in vivo* data.

713. Between the time that REDAC the ’963 provisional application and the ’964 provisional application, REDACTED

714. REDACTED to the PTO, but intentionally, and with deceptive intent, excluded the most relevant REDACTED

715. In December 2005, Supernus was established after acquiring substantially all of the assets of Shire.

716. Around 2000, Shire contacted Plaintiff GLI's predecessor-in-interest, CollaGenex Pharmaceuticals, Inc. ("CollaGenex"), regarding a potential collaboration between the parties in which Shire would develop a once-daily formulation of Periostat® (20 mg doxycycline indicated for twice daily administration).

717. CollaGenex had previously obtained FDA approval to market 20-mg doxycycline-hyclate capsules under the brand name Periostat® on or around September 30, 1998 pursuant to New Drug Application No. 50-744.

718. As of September 30, 1998, NDA No. 50-744 was held by CollaGenex.

719. According to its labeling, Periostat® is administered twice daily at 12 hour intervals, for a total daily dose of 40 mg of doxycycline hyclate.

720. CollaGenex subsequently submitted New Drug Application No. 50-783, which sought to market a 20 mg tablet version of Periostat®, to be taken twice-daily.

721. FDA approved that application on or about February 2, 2001.

722. As of February 2, 2001, NDA No. 50-783 was held by CollaGenex.

723. CollaGenex formally engaged Shire to develop a once-daily formulation of Periostat®.

724. CollaGenex and Shire entered into certain agreements, including a "Development Agreement" dated May 22, 2001, and a "Development and Licensing Agreement" dated June 10, 2002.

725. The initial focus of this engagement called for Shire to develop a 40-mg doxycycline product that resulted in certain doxycycline blood levels when administered once daily.

726. Shire retained all patent rights to any doxycycline product it was engaged to develop.

727. REDACTED owed a duty of candor and good faith in dealing with the PTO. *See* 37 C.F.R. § 1.56(a).

728. The disclosure of the '963 provisional application includes six Examples and four Figures, including computer-simulated pharmacokinetic ("PK") profiles.

729. The '963 provisional application describes certain simulated blood level profiles determined by *in silico* modeling that, in turn, relied in part upon certain data from human clinical trials.

730. The '963 provisional application does not contain data from any in vivo PK studies involving the claimed doxycycline formulation.

731. A PK study is designed to measure the levels of drug and metabolites in the body at a particular time or during a particular timeframe.

732. REDACTED

733. A PK steady-state study is designed to measure the levels of drugs and metabolites in the body after steady-state is achieved (*i.e.*, when the rates of drug administration and drug elimination are equal).

734. In or around the Spring of 2003, Shire developed a prototype 40 mg formulation comprised of 75% immediate-release ("IR") beadlets (30 mg doxycycline) and 25% delayed-release beadlets (10 mg doxycycline) ("the 75/25 IR/DR Formulation").

735. REDACTED CollaGenex commissioned a PK study—REDACTED RE—to compare the 75/25 IR/DR Formulation, referred to at times as "Shire's Prototype Formulation," administered orally once a day with the prior-art Periostat® administered orally twice a day.

736. The REDACTED compared a once daily oral dose of a 30 mg IR, 10 mg DR doxycycline monohydrate capsule formulation versus a twice daily oral dose of Periostat® (doxycycline hyclate tablets), 20 mg, in normal healthy, male and female volunteers.

737. Prior to the study start date of a Clinical Phase I study sponsored by CollaGenex on or about July 14, 2003, Shire developed a 30 mg IR, 10 mg DR doxycycline monohydrate capsule formulation.

738. The REDACTED study reported on several PK parameters, including Cmax, Cmin, tmax, and area under the curve ("AUC").

739. Cmax refers to the peak plasma concentration that a drug achieves in a specific time frame after a drug has been administered and prior to the administration of a second dose.

740. Cmin is the lowest concentration a drug achieves after dosing. tmax represents the time to reach Cmax.

741. AUC describes the area or arithmetic product under a concentration curve for a given dose of a drug and for a given time.

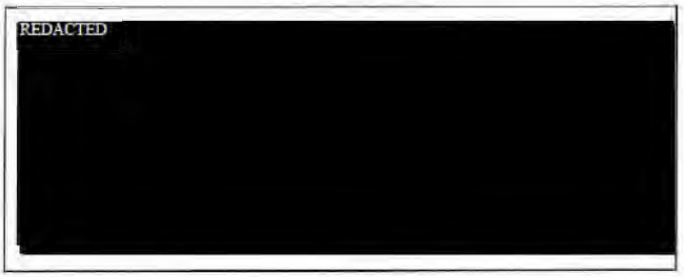
742. The results of REDACTED

743. REDACTED

744. The findings of the REDACTED Study were described in a final clinical study report dated January 14, 2004, titled, "An Open Label, Randomized, Two Treatment, Two Way Crossover, Pharmacokinetic Study to Compare an Extended Release Doxycycline Capsule (40 mg) Administered Orally Once Daily (QD) for Seven Days Versus Periostat® Tablets (20 mg) Administered Orally Twice Daily Twelve Hours Apart (BID) for Seven Days in Normal Healthy and Female Volunteers."

745. On Sept. 11, 2003, CollaGenex forwarded Shire data from the REDACTED

746. A Shire employee used REDACTED



747. On September 11, 2003, [redacted] of Shire with the subject: "[redacted] and with an attachment thereto that, *inter alia*, contained [redacted]

748. [redacted]

749. [redacted]

750. [redacted] received the [redacted] from a Shire employee for the purpose of including that information in the '964 provisional application and the non-provisional application that later issued as the '532 patent, and to which the '740 patent claims priority.

751. [redacted] included some information from [redacted] in the '964 provisional application and the non-provisional application that later issued as the '532 patent.

752. On February 26, 2004, [redacted] filed the '964 provisional application.

753. On April 7, 2004, REDACTED filed the ’620 application, which later issued as the ’532 patent.

754. The '964 provisional application and '620 application as filed contain Table 1 as recited below:

Table 1

	75/25 IR/DR Day 1	75/25 IR/DR Day 7 steady state	Periostat® Day 1
T_{max}	2.2	2.3	1.9/11.9
C_{max}	562	602	100/333
AUC_{0-24}(Hr*ng/ml)	5388	7230	4280

755. The '964 provisional application and the '620 application as filed contain an Example 7 and an Example 8.

756. The ’963 provisional application as filed does not contain an Example 7 or an Example 8.

757. Example 7 of the ’964 provisional application and the ’620 application as filed describes a 30 mg IR, 10 mg DR doxycycline capsule formulation.

758. Table 1 of Example 8 of the ’964 provisional application and the '620 application as filed relates to certain data gathered during the course of REDACTED

759. The ’532 and ’740 patents contain Table 1 as recited below:

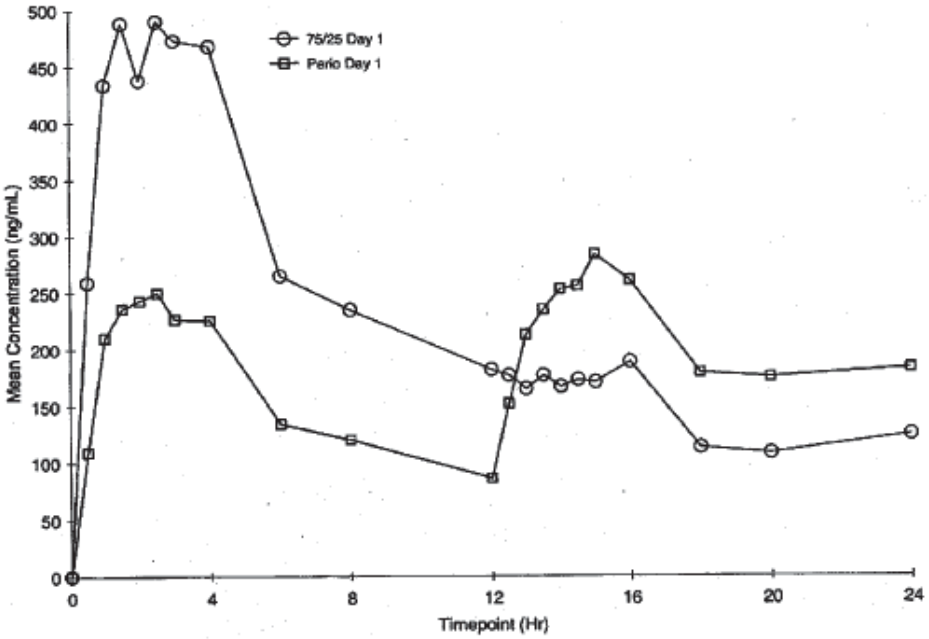
TABLE 1

	75/25 IR/DR Day 1	75/25 IR/DR Day 7 steady state	Periostat ® Day 1
T_{max}	2.2	2.3	1.9/11.9
C_{max}	562	602	100/333
AUC_{0-24}(Hr*ng/ml)	5388	7230	4280

760. The ’964 provisional application and the ’620 application contains Figure 6 as recited below:

Figure 6
Doxycycline Steady State Study

Comparison of 75/25 IR/DR (40 mg) to Periostat (20 mg BID) at Day 1
(PK Curves from Mean Plasma Concentrations)



761. The ’964 provisional application and the ’620 application as filed recite, in part, “Figure 6 compares the PK profiles of the 75:25 40 mg once daily dosage form and the Periostat® 20 mg (twice daily) dosage forms.”

762. REDACTED the ’964 provisional application and the ’620 application, REDACTED owed a duty of candor and good faith in dealing with the PTO. *See* 37 C.F.R. § 1.56(a).

763. The ’964 provisional application and the ’620 application both include an Example 7 and an Example 8, which do not appear in the ’963 provisional application.

764. Example 7 describes the Shire Prototype Formulation, and Example 8 summarizes REDACTED

765. The data from REDACTED is summarized in Table 1 of Example 8, which is reproduced below:

TABLE 1

	75/25 IR/DR Day 1	75/25 IR/DR Day 7 steady state	Periostat® Day 1
T_{max}	2.2	2.3	1.9/11.9
C_{max}	562	602	100/333
AUC_{0-24}(Hr*ng/ml)	5388	7230	4280

766. REDACTED created Table 1 of the '532 and '740 patents from REDACTED REDACTED

767. REDACTED

REDACTED

REDACTED

TABLE 1

	75/25 IR/DR Day 1	75/25 IR/DR Day 7 steady state	Periostat® Day 1
T_{max}	2.2	2.3	1.9/11.9
C_{max}	562	602	100/333
AUC_{0-24}(Hr*ng/ml)	5388	7230	4280

Table 1 from the '532 and '740 Patents

768. The statistical analysis that directly compared the 75/25 IR/DR Formulation to the prior-art Periostat® product was also excluded.

769. Ms. Lane also included Figure 6 in the '964 provisional application and the non-provisional application that issued as the '532 patent.

770. Figure 6 is described as "compar[ing] the PK profiles of the 75:25 once-daily dosage form and the Periostat® 20 mg (twice daily) dosage forms."

771. Figure 6, like Table 1, provides only a comparison on Day 1 before steady-state was achieved.

772. The withheld REDACTED is both but-for material and material as affirmative egregious misconduct.

773. The withheld REDACTED is but-for material because it demonstrates that, REDACTED

774. The PTO Examiner's stated reason for allowing the claims of the '532 patent was that "the closest prior art" did "not teach or fairly suggest dosage forms comprising about 40 mg doxycycline." But that is precisely what Periostat® administered twice a day provides—a 40-mg daily dose of doxycycline. And the withheld REDACTED "give[s] steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml," as recited by all the asserted claims.

775. If the Examiner had the benefit of reviewing REDACTED intentionally withheld), the Examiner would have realized that the prior art teaches the very thing he said it did not—a 40-mg daily dose of doxycycline that achieves the claimed steady-state doxycycline blood levels.

776. REDACTED only presented the Examiner with Day 1 PK data for Periostat® and the comparisons that suggested the claimed invention to be different from the prior art.

777. The Examiner would not have allowed the claims of the '532 patent—and, by extension, the claims of the '740 patent—if REDACTED

778. During prosecution of the application that issued as the '532 patent, the patentee also distinguished the claimed invention over the prior art because the claimed invention purportedly failed to disclose "a composition, which at a once-daily dosage will give steady state

blood levels of doxycycline of a minimum of about 0.1 µg/ml and a maximum of about 1.0 µg/ml."

779. The [redacted]

780. The [redacted] is also *per se* material because [redacted] act of withholding it is affirmative egregious misconduct.

781. The only meaningful difference between the [redacted] and Table 1 of the Chang Patents is [redacted]

782. [redacted] affirmative act of intentionally removing [redacted] and presenting incomplete information to the PTO is *per se* material.

783. [redacted] intentionally removed [redacted] and she did so with deceptive intent.

784. [redacted] received [redacted] from another Shire employee.

785. [redacted] created Table 1 of the '532 patent from [redacted]

786. [redacted] elected not to include [redacted] '532 patent.

787. [redacted] has neither denied that [redacted] nor offered any good-faith explanation for why it was not included [redacted] of the '532 patent.

788. As between [redacted] is the most relevant because [redacted] claims of the '532 and '740 patents.

789. CollaGenex relied on REDACTED data in its NDA 50-805 to the FDA.

790. CollaGenex used REDACTED data to assert to the FDA REDACTED REDACTED

791. CollaGenex shared this information with Shire.

792. REDACTED was not as forthright with the PTO, acting contrary to CollaGenex's representations to the FDA, REDACTED selectively presented the PTO with only the Periostat® Day 1 data, REDACTED

793. In creating Table-1 in the patents from the data obtained from REDACTED REDACTED actively REDACTED

794. Whereas the Periostat® Day 1 data may suggest that the 75/25 IR/DR Formulation and Periostat® might be distmct because on Day 1 the 75/25 IR/DR Formulation resulted in doxycycline blood levels that were "significantly higher" than Periostat®, REDACTED

795. REDACTED thus, with deceptive intent provided the PTO only with REDACTED but she intentionally withheld REDACTED

796. By withholding REDACTED intentionally concealed REDACTED with respect to the claimed formulation.

B. Plaintiffs Breached the Terms of the Amneal OCA by Permitting REDACTED to Participate in Patent Prosecution Activities.

797. REDACTED

798. On September 27, 2011, Amneal sent a Notice of Paragraph IV Certification of U.S. Patent Nos. 5,789,395; 5,919,775; 7,211,267; 7,232,572 and 7,749,532 Concerning ANDA 203278 for Doxycycline Oral Capsule, 40 mg ("Notice Letter").

799. Amneal's Notice Letter was addressed to GLLP, GLI, The Research Foundation of State University of New York, New York University, and Supernus, and recited in pertinent part:

> Pursuant to 21 U.S.C. § 355(j)(5)(C), this notice letter includes an Offer of Confidential Access to Application. As required by §355(j)(5)(C)(i), AMNEAL offers to provide confidential access to certain information from its ANDA No. 203278 for the sole and exclusive purposed of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) can be brought.
>
> Section 355(j)(5)(C)(i)(III) allows AMNEAL to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants AMNEAL the right to redact its ANDA in response to a request for Confidential Access under this offer.

800. Specifically, Amneal offered to provide confidential access to certain information from its ANDA 203278 "for the sole and exclusive purpose of determining whether an infringement action referred to in [21 U.S.C.] § 355(j)(5)(B)(iii) can be brought."

801. Amneal's OCA also included a patent-prosecution bar, which states:

> Amneal will permit confidential access to certain information from its proprietary ANDA No. 203278 to attorneys from one outside law firm representing the NDA holder and the Patent holders; ***provided, that attorneys from such firm do not engage, formally or informally, in patent prosecution for the NDA holder or the Patent holders***. Such information (hereinafter, "Confidential Amneal Information") shall be marked with the legend "CONFIDENTIAL."

802. The purpose of a patent-prosecution bar is to avoid the risk that a disclosing party's confidential information will be used, inadvertently or otherwise, in connection with patent-prosecution activities.

803. On October 4, 2011, REDACTED expressly accepted this OCA on behalf of Plaintiffs, stating "[p]ursuant to the Offer of Confidential Access accompanying the notice letter, please forward a copy of the ANDA so that I may evaluate the claims made in the letter and attached detailed statement."

804. REDACTED request for access to Amneal's ANDA No. 203278 is, by statute, "considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access . . . ." 21 U.S.C. § 355(j)(5)(C)(i)(III).

805. By accepting the terms of the OCA on behalf of Plaintiffs, REDACTED was contractually obligated to abide by the agreed-upon terms of the OCA.

806. Amneal relied on REDACTED representations that Amneal's confidential information contained in its ANDA No. 203278 would be used for the sole and limited purpose of evaluating possible infringement of the patents, in accordance with the statutory scheme. *See* 35 U.S.C. § 355(j)(5)(C)(i)(III).

807. Based on REDACTED representations, Dennies Varughese sent a letter, dated October 11, 2011, containing the reference line "ANDA No. 20-3278 for Doxycycline Capsules, 40 mg; Ref No.:2927.019LIT0," REDACTED which recites in part:

> Pursuant to the Offer of Confidential Access ("OCA") accompanying Amneal Pharmaceutical's Notice of Paragraph IV Certification of United States Patent Nos. 5,789,395; 5,919,775; 7,211,267; 7,232,572 and 7,749,532 dated September 27, 2011, to Galderma Laboratories L.P.; Galderma Laboratories, Inc.; Research Foundation of State University of New York; New York University; and Supernus Pharmaceuticals, Inc. (collectively "Galderma"), please find enclosed a disc containing Amneal's entire ANDA No. 20-3278 for Doxycycline Capsules, 40mg ("the ANDA").
>
> This production of the ANDA and any use thereof by Galderma are governed by the OCA, all terms of which Galderma has agreed

> to abide by as indicated in your letter of October 4, 2011, and confirmed in your email dated October 7, 2011. As such, the disc has been marked "CONFIDENTIAL—PURSUANT TO OFFER OF CONFIDENTIAL ACCESS," and all parts contained therein should be treated as such.

808. Mr. Varughese's October 11, 2011 letter enclosed information from Amneal's ANDA No. 203278.

809. On August 27, 2012, Plaintiffs responded to Amneal's First Set of Interrogatories (No. 1), stating, in part, REDACTED [redacted]

810. On December 10, 2012, Plaintiffs provided Amneal with their privilege log, which contains certain entries dated after October 4, 2011, REDACTED [redacted]

811. On August 12, 2011, a document regarding the '676 application signed by Sunit Talapatra of Foley & Lardner entitled "Amendment and Reply Under 37 C.F.R. § 1.111" was filed with the PTO, which states in part: "Hence, upon entry of this paper, Claims 26-61 and 63-65 were pending in the subject case with claims 49-61 and 63-65 under active consideration."

812. On March 13, 2012, a document regarding the '676 application signed by Sunit Talapatra of Foley & Lardner titled, "Amendment Under 37 CFR 1.116" was filed with the PTO, which states in part:

> Claims 26-61 and 63-65 were pending in the subject case. All of these claims have been canceled in favor of claims 66-94, being newly added. Hence, upon entry of this paper, claims 66-94 will remain pending.

813. Claims 66-94 of the '676 application were later issued as claims 1-29 of the '740 patent.

814. REDACTED

815. During the time that REDACTED

816. Contrary to the statutory scheme and REDACTED acceptance of the express terms of the OCA, REDACTED as confirmed by Plaintiffs' response to Amneal's Interrogatory No. 1, which states that REDACTED

817. Numerous entries in Plaintiffs' December 10, 2012 Privilege Log state— REDACTED each of these entries is dated after REDACTED

818. Plaintiffs' violation of the OCA has harmed and prejudiced Amneal and also deprived Amneal of the contractual benefits contemplated by the Amneal OCA; namely, that nobody who received access to Amneal's confidential information would be in a position to informally or formally assist in the prosecution of Plaintiffs' pending patent applications.

C. Plaintiffs' Claims of Infringement of the '740 Patent are Barred by their Unclean Hands

819. Before REDACTED obtained access to Amneal's confidential information, Plaintiffs' patent-prosecution counsel were prosecuting application claims 49-61, 63-65 in U.S. Application No. 12/155,676 ("the '676 application").

820. It was not until after REDACTED obtained access to Amneal's confidential information REDACTED that Plaintiffs' patent-prosecution counsel canceled all then-pending claims and added an entirely new set of claims (*i.e.*, application claims 66-94).

821. These new application claims differed substantially from the previously pending claims, *i.e.*, application claims 66-94 were renumbered and later issued as claims 1-29 of the '740 patent.

822. REDACTED and violations of the OCA were conducted in bad faith in order to obtain new patent claims and thereby give Plaintiffs an unfair litigation advantage.

823. REDACTED also violated the prosecution bar set forth in the Court's Protective Order.

824. Plaintiffs' lead trial counsel acknowledged to this Court during the Markman hearing that Plaintiffs benefitted from the issuance of the '740 patent (Chang II) claims because those claims do not have certain limitations contained in the '532 patent (Chang I) claims, stating:

> [Y]ou shouldn't be concerned [that Plaintiffs will argue that Amneal's single delayed-release tablet is literally the same as the claimed delayed-release pellets in Chang I] because [Amneal] infringe[s] Chang II no matter what you do. I'm sorry, but just to be sincere, I think it's important to point that out. We don't have any of these limitations in Chang II.

Nov. 30, 2012 Claim Construction Hearing at 83:7-11.

825. And Plaintiffs' lead trial counsel made similar statements to this Court during the June 12, 2012 hearing for Plaintiffs' Motion for Stay:

> [Amneal's] noninfringement argument, their one hope regarding the Chang patent which they say sets them apart from every other generic defendant, isn't going to apply for very long, even if it were to apply.

> A continuation of the Chang patent is going to be issuing within the next few weeks. The notice of allowance has already been obtained. And it does not contain the limitation that they're resting their hopes on for this noninfringement argument.

June 12, 2012 Motion for Stay Hearing at 21:4-12.

826. As set forth above, Plaintiffs' patent-prosecution counsel did not seek the claims that later issued in the '740 patent (*i.e.*, Chang II) until after REDACTED violated Amneal's OCA.

827. REDACTED acted at all relevant times as the agent of Plaintiffs and REDACTED misconduct inured to the direct benefit of Plaintiffs.

EXHIBIT 4

EXHIBIT 4 OF PROPOSED JOINT PRETRIAL ORDER
PLAINTIFFS' ISSUES OF LAW TO BE LITIGATED AT TRIAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES INC., GALDERMA LABORATORIES, L.P. and SUPERNUS PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	C.A. No. 11-1106 (LPS)
v.	)	REDACTED
AMNEAL PHARMACEUTICALS, LLC. and AMNEAL PHARMACEUTICALS CO. (I) PVT. LTD.,	)	
Defendants.	)	

PLAINTIFFS' ISSUES OF LAW TO BE LITIGATED AT TRIAL

Plaintiffs respectfully submit the following list of issues of law that remain to be litigated. Should the Court determine that any issue identified in this list is more properly considered an issue of fact, it shall be so considered. Plaintiffs reserve the right to revise this list in light of the Court's rulings and in light of Amneal's lists of issues of law and fact to be litigated.

I. U.S. PATENT NO. 7,749,532

A. Infringement Of The Chang '532 Patent

1. Whether Amneal has infringed or will infringe any of claims 1-8 and 15-21 of the Chang '532 patent ("asserted claims of the Chang '532 patent").

2. Whether Amneal has induced or will induce infringement of any of the asserted claims of the Chang '532 patent.

3. Whether Amneal has contributed to or will contribute to the infringement of any of the asserted claims of the Chang '532 patent.

B. Validity Of The Chang '532 Patent

4. Whether Amneal can prove by clear and convincing evidence that each of the asserted claims of the Chang '532 patent that Amneal is found to infringe is invalid.

i. Presumption Of Validity

5. Whether Amneal can overcome, by clear and convincing evidence, the presumption that the asserted claims of the Chang '532 patent are valid.

ii. Prior Art

6. Whether Amneal can prove by clear and convincing evidence that each reference asserted against the Chang '532 patent is "prior art" under 35 U.S.C. § 102 and/or § 103.

iii. Novelty

7. Whether Amneal can prove by clear and convincing evidence that any prior art reference asserted by Amneal (1) discloses each and every element, either expressly or inherently, of any of the asserted claims of the Chang '532 patent, and (2) does so in a way that would have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation as of the time of the invention.

8. To the extent Amneal argues that any claim limitation of any of the asserted claims of the Chang '532 patent is inherent in any alleged prior art reference asserted by Amneal, whether Amneal can prove by clear and convincing evidence that each such claim limitation is necessarily present in the alleged prior art reference.

9. Whether Amneal can prove by clear and convincing evidence that the 30 mg immediate release ("IR"), 10 mg delayed release ("DR") doxycycline ratio claimed in the Chang '532 patent is not critical or central to the operation of the claimed inventions of the asserted claims of the Chang '532 patent. *See OSRAM Sylvania, Inc., v. American Induction Technologies, Inc.*, 701 F.3d 698, 705-06 (Fed. Cir. 2012); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2001).

10. Whether Amneal can prove by clear and convincing evidence that the different 40 mg IR/DR doxycycline ratios between the range of 40 mg IR, 0 mg DR and 0 mg IR, 40 mg DR would not operate differently. *See OSRAM Sylvania*, 701 F.3d at 705-06.

iv. Non-Obviousness

11. Whether Amneal can prove by clear and convincing evidence that the differences between the subject matter of any of the asserted claims of the Chang '532 patent and any asserted prior art references relied on by Amneal (alone or in combination) are such that any of

the asserted claims of the Chang '532 patent would have been obvious to a person of ordinary skill in the art. *See, e.g., Kinetic Concepts v. Smith & Nephew, Inc.* 688 F.3d 1342, 1366 (Fed. Cir. 2012); *In re Baker Hughes Inc.*, 215 F.3d 1297, 1303-04 (Fed. Cir. 2000).

12. Whether Amneal can prove by clear and convincing evidence that the invention described in any of the asserted claims of the Chang '532 patent was obvious to a person of ordinary skill in the art at the time of the invention in light of (1) the scope and content of the alleged prior art; (2) the differences between such claim and the alleged prior art; (3) the level of ordinary skill in the art at that time; and (4) the objective evidence of non-obviousness. *See, e.g., Kinetic* Concepts, 688 F.3d at 1360; *Baker Hughes*, 215 F.3d at 1301; *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986).

13. Whether Amneal can prove by clear and convincing evidence each fact forming the factual foundation upon which it alleges that any of the asserted claims of the Chang '532 patent are obvious.

14. Whether Amneal can prove by clear and convincing evidence that a person of ordinary skill in the art would have had any reason or motivation to combine the alleged prior art. *See Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) ("Even when all claim limitations are found in prior art references, the fact-finder must determine . . . whether there was motivation to combine teachings from separate references."); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012) (party asserting obviousness must show that "a skilled artisan would have had a reason to combine the prior art references to achieve the claimed invention").

15. Whether Amneal can prove by clear and convincing evidence that a person of ordinary skill in the art provided with the alleged prior art would have reasonably expected the claimed inventions of the asserted claims of the Chang '532 patent to succeed in achieving their intended purpose. *See Cyclobenzaprine*, 676 F.3d at 1068-69; *Broadcom Corp. v. Emulex Corp*., 732 F.3d 1325, 1335 (Fed. Cir. 2013).

16. Whether objective indicia of non-obviousness exist with respect to the inventions claimed in the asserted claims of the Chang '532 patent. *See infra* Section III ("Objective Indicia of Non-Obviousness"); *see also Institut Pasteur v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013); *Cyclobenzaprine*, 676 F.3d at 1075-76; *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010).

C. Enforceability In Light Of Amneal's Inequitable Conduct Defense

17. Whether Amneal can separately prove, by clear and convincing evidence that during the prosecution of the Chang '532 patent before the U.S. Patent and Trademark Office ("PTO"), the patentee both (1) withheld any allegedly material information from the PTO, and (2) did so with a specific intent to deceive. *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1290 (Fed. Cir. 2011).

18. Whether Amneal can prove by clear and convincing evidence that any allegedly undisclosed information is "but-for material," *i.e.*, that the PTO would not have allowed any of the asserted claims of the Chang '532 patent if it had been aware of such allegedly undisclosed information. *See id.* at 1291.

19. Whether Amneal can prove by clear and convincing evidence that any alleged nondisclosure of information to the PTO during prosecution of the Chang '532 patent constituted an act of "affirmative egregious misconduct." *See Outside the Box Innovations, LLC v. Travel*

Caddy, Inc., 695 F.3d 1285, 1294 (Fed. Cir. 2012); *Senju Pharm. Co.. Ltd. v. Apotex, Inc.*, 921 F. Supp.2d 297, 308 n.15 (D. Del. 2013) ("Omissions, however, cannot constitute affirmative egregious misconduct.")

20. Whether Amneal can prove by clear and convincing evidence that the patentee acted with specific intent to deceive the PTO. *See Therasense*, 649 F.3d at 1290.

21. Whether Amneal can prove by clear and convincing evidence that the patentee knew of the allegedly undisclosed information, knew that the allegedly undisclosed information was "but-for material," and made a deliberate decision to withhold the allegedly undisclosed information. *See id.*

22. Whether Amneal can prove by clear and convincing evidence that an inference of a specific intent to deceive the PTO is the single most reasonable inference able to be drawn from the evidence. *See id.* (citing *Star Scientific Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008)).

23. Whether the evidence presented by Amneal is sufficient to require a finding of deceitful intent in light of all the circumstances. *Id.* (citing *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 873 (Fed. Cir. 1988)).

II. U.S. PATENT NO. 8,206,740

A. Infringement Of The Chang '740 Patent

24. Whether Amneal has infringed or will infringe any of claims 1, 2, 6-15, and 19-22 of the Chang '740 patent ("asserted claims of the Chang '740 patent").

25. Whether Amneal has induced or will induce infringement of any of the asserted claims of the Chang '740 patent.

26. Whether Amneal has contributed to or will contribute to the infringement of any of the asserted claims of the Chang '740 patent.

B. Validity Of The Chang '740 Patent

27. Whether Amneal can prove by clear and convincing evidence that each of the asserted claims of the Chang '740 patent that Amneal is found to infringe is invalid.

i. Presumption Of Validity

28. Whether Amneal can overcome, by clear and convincing evidence, the presumption that the asserted claims of the Chang '740 patent are valid.

ii. Prior Art

29. Whether Amneal can prove by clear and convincing evidence that each reference asserted against the Chang '740 patent is "prior art" under 35 U.S.C. § 102 and/or § 103.

iii. Novelty

30. Whether Amneal can prove by clear and convincing evidence that any prior art reference asserted by Amneal (1) discloses each and every element, either expressly or inherently, of any of the asserted claims of the Chang '740 patent, and (2) does so in a way that would have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation as of the time of the invention.

31. To the extent Amneal argues that any claim limitation of any of the asserted claims of the Chang '740 patent is inherent in any alleged prior art reference asserted by Amneal, whether Amneal can prove by clear and convincing evidence that each such claim limitation is necessarily present in the alleged prior art reference.

32. Whether Amneal can prove by clear and convincing evidence that the 30 mg IR, 10 mg DR doxycycline ratio claimed in the Chang '532 patent is not critical or central to the

operation of the claimed inventions of the asserted claims of the Chang '532 patent. *See OSRAM Sylvania*, 701 F.3d at 705-06; *see also Atofina*, 441 F.3d at 999.

33. Whether Amneal can prove by clear and convincing evidence that the different 40 mg IR/DR doxycycline ratios between the range of 40 mg IR, 0 mg DR and 0 mg IR, 40 mg DR would not operate differently. *See OSRAM Sylvania*, 701 F.3d at 705-06.

iv. Non-Obviousness

34. Whether Amneal can prove by clear and convincing evidence that the differences between the subject matter of any of the asserted claims of the Chang '740 patent and any asserted prior art references relied on by Amneal (alone or in combination) are such that any of the asserted claims of the Chang '740 patent would have been obvious to a person of ordinary skill in the art. *See, e.g.*, *Kinetic Concepts*, 688 F.3d at 1366; *Baker Hughes*, 215 F.3d at 1303-04.

35. Whether Amneal can prove by clear and convincing evidence that the invention described in any of the asserted claims of the Chang '740 patent was obvious to a person of ordinary skill in the art at the time of the invention in light of (1) the scope and content of the alleged prior art; (2) the differences between such claim and the alleged prior art; (3) the level of ordinary skill in the art at that time; and (4) the objective evidence of non-obviousness. *See, e.g.*, *Kinetic Concepts*, 688 F.3d at 1366; *Baker Hughes*, 215 F.3d at 1303-04; *Bausch & Lomb*, 796 F.2d at 448.

36. Whether Amneal can prove by clear and convincing evidence each fact forming the factual foundation upon which it alleges that any of the asserted claims of the Chang '740 patent are obvious.

37. Whether Amneal can prove by clear and convincing evidence that a person of ordinary skill in the art would have had any reason or motivation to combine the alleged prior art. *See, e.g.*, *Cheese Sys.*, 725 F.3d at 1352 ("Even when all claim limitations are found in prior art references, the fact-finder must determine . . . whether there was motivation to combine teachings from separate references."); *Cyclobenzaprine*, 676 F.3d at 1068-69 (party asserting obviousness must show that "a skilled artisan would have had a reason to combine the prior art references to achieve the claimed invention").

38. Whether Amneal can prove by clear and convincing evidence that a person of ordinary skill in the art provided with the alleged prior art would have reasonably expected the claimed inventions of asserted claims of the Chang '740 patent to succeed in achieving their intended purpose. *See Cyclobenzaprine*, 676 F.3d at 1068-69; *Broadcom*, 732 F.3d at 1335.

39. Whether objective indicia of non-obviousness exist with respect to the inventions claimed in the asserted claims of the Chang '740 patent. *See infra* Section III ("Objective Indicia of Non-Obviousness"); *see also Institut Pasteur*, 738 F.3d at 1346; *Cyclobenzaprine*, 676 F.3d at 1075-76; *Crocs*, 598 F.3d at 1310.

C. Enforceability Of The Chang '740 patent in Light of Amneal's Inequitable Conduct Defense

40. Whether Amneal can separately prove, by clear and convincing evidence, that during the prosecution of the Chang '740 patent before the PTO, the patentee both (1) withheld any material reference from the PTO, and (2) did so with a specific intent to deceive. *Therasense*, 649 F.3d at 1290.

41. Whether Amneal can prove by clear and convincing evidence that any allegedly undisclosed information is "but-for material," *i.e.*, that the PTO would not have allowed any of

the asserted claims of the Chang '740 patent if it had been aware of such allegedly undisclosed information. *Id.* at 1291.

42. Whether Amneal can prove by clear and convincing evidence that any alleged nondisclosure of information to the PTO during prosecution of the Chang '740 patent constituted an act of "affirmative egregious misconduct." *See Outside the Box*, 695 F.3d at 1294; *Senju*, 921 F. Supp. 2d at 308 n.15 ("Omissions, however, cannot constitute affirmative egregious misconduct.")

43. Whether Amneal can prove by clear and convincing evidence that the patentee acted with specific intent to deceive the PTO. *See Therasense*, 649 F.3d at 1290.

44. Whether Amneal can prove by clear and convincing evidence that the patentee knew of the allegedly undisclosed information, knew that the allegedly undisclosed information was "but-for material," and made a deliberate decision to withhold the allegedly undisclosed information. *See id.*

45. Whether Amneal can prove by clear and convincing evidence that an inference of a specific intent to deceive the PTO is the single most reasonable inference able to be drawn from the evidence. *See id.* (citing *Star Scientific*, 537 F.3d at 1366 (Fed. Cir. 2008)).

46. Whether the evidence presented by Amneal is sufficient to require a finding of deceitful intent in light of all the circumstances. *See id.* (citing *Kingsdown*, 863 F.2d at 873).

D. Enforceability With Respect To Amneal Of The Chang '740 Patent In Light of Amneal's Unclean Hands Allegations

47. Whether Amneal can prove by clear and convincing evidence that Galderma's REDACTED has engaged in conduct involving fraud, deceit, unconscionability, or bad faith. *See Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 343 F. Supp. 2d 272, 321-22 (D. Del. 2004).

48. Whether Amneal can prove by clear and convincing evidence that REDACTED alleged conduct has an immediate and necessary relationship to the equity sought by Plaintiffs in this litigation. *See id.*

49. Whether Amneal can prove by clear and convincing evidence that REDACTED alleged conduct resulted in any injury to Amneal. *See Domus, Inc. v. Davis-Giovinazzo Constr. Co.*, C.A. No. 10-1654, 2011 WL 3666485, at *8-*10 (E.D. Pa. Aug. 22, 2011); *Pharmacia Corp. v. GlaxoSmithKline Consumer Healthcare, L.P.*, 292 F. Supp. 2d 594, 610 (D.N.J. 2003).

50. Whether Amneal can prove that information within Amneal's September 27, 2011 Paragraph IV Notice Letter is confidential and is not deemed a public disclosure. *See Nycomed US Inc. v. Tolmar, Inc.*, C.A. No. 10-2635, 2011 WL 1675027, at *7-*8 (D.N.J. Apr. 28, 2011) (stating that "the information disclosed in [a] Paragraph IV Notice Letter is . . . part of 'an inherently public process' and therefore constitutes a public disclosure"); *see also* 68 Fed. Reg. 36676, at 36690 (June 18, 2003).

51. **[*Plaintiffs reserve the right to supplement their Issues of Law to be Litigated at Trial with respect to Amneal's allegations regarding unclean hands, for which discovery requested by Defendants is presently ongoing.]***

E. Enforceability With Respect To Amneal Of The Chang '740 Patent In Light Of Amneal's Breach Of Contract Allegations

52. Whether Amneal can separately prove that (1) Galderma's REDACTED breached the Offer of Confidential Access ("OCA") in Amneal's September 27, 2011 Paragraph IV Notice Letter, and (2) Amneal suffered damages resulting from any alleged breach. *See Stratton Group, Ltd. v. Sprayregen*, 458 F. Supp. 1216, 1217-18 (S.D.N.Y. 1978).

53. Whether Amneal can prove that REDACTED alleged breach of contract caused Amneal damages. *See, e.g., Cornell University et al. v. Illumina, Inc.*, C.A. No. 10-433, 2012 WL 1885129, at *4-*5 (D. Del. May 23, 2012) (dismissing breach of contract counterclaim for failure to show damages); *Adamson v. Bachner*, C.A. No. 99-cv-3741, 2000 WL 702913, at *2-*3 (S.D.N.Y. May 31, 2000) (dismissing, *inter alia*, breach of contract claim because no damages resulted from the party's alleged misconduct).

54. Whether Amneal can prove that REDACTED alleged breach of contract directly and proximately caused damage to Amneal. *See Diesel Props S.R.L. v. Greystone Bus. Credit II LLC*, 631 F.3d 42, 52-53 (2d Cir. 2011).

55. Whether Amneal can prove that information that can be found within Amneal's September 27, 2011 Paragraph IV Notice Letter is confidential and is not deemed a public disclosure. *See Nycomed US Inc. v. Tolmar, Inc.*, C.A. No. 10-2635, 2011 WL 1675027, at *7-*8 (D.N.J. Apr. 28, 2011) (stating that "the information disclosed in [a] Paragraph IV Notice Letter is . . . part of "an inherently public process" and therefore constitutes a public disclosure"); *see also* 68 Fed. Reg. 36676, at 36690 (June 18, 2003).

56. **[*Plaintiffs reserve the right to supplement their Issues of Law to be Litigated at Trial with respect to Amneal's allegations regarding breach of contract, for which discovery requested by Defendants is presently ongoing.*]**

III. OBJECTIVE INDICIA OF NON-OBVIOUSNESS

57. Whether any objective indicia of non-obviousness exist with respect to the inventions of any of the asserted claims of the '532 and the Chang '740 patents ("the Chang patents"). *See Crocs*, 598 F.3d at 1310 (objective indicia of non-obviousness "can be the most probative evidence of non-obviousness in the record, and enables the . . . court to avert the trap

of hindsight."); *see also Institut Pasteur*, 738 F.3d at 1346 ("Objective indicia of non-obviousness may often establish that an invention appearing to have been obvious in light of the prior art was not.")

58. Whether Oracea® is a commercial success.

59. Whether there is a nexus between the commercial success of Oracea® and the inventions of any of the asserted claims of the Chang patents.

60. Whether Amneal has rebutted Plaintiffs' *prima facie* case of nexus by providing evidence that the commercial success of Oracea® is due to factors that are not related to the inventions of any of the asserted claims of the Chang patents.

61. Whether Amneal has rebutted Plaintiffs' *prima facie* case of nexus by providing evidence that market entry was blocked by any patent prior to the critical date of the Chang patents. *See Eli Lilly & Co. v. Sicor Pharms., Inc.*, 705 F. Supp. 2d 971, 1007 n.47 (S.D. Ind. 2010); *see also Janssen Pharms., Inc. v. Watson Labs, Inc.*, C.A. No. 08-5103, 2012 WL 3990221, at *23 (D.N.J. Sept. 11, 2012).

62. Whether the Chang patents or the commercial embodiment thereof, Oracea®, have received recognition and acceptance in the industry.

63. Whether others have tried and failed to solve the problems that were solved by the inventions of any of the asserted claims of the Chang patents.

64. Whether the inventions of any of the asserted claims of the Chang patents have fulfilled a long-felt need.

65. Whether the inventions of any of the asserted claims of the Chang patents possess unexpected benefits.

66. Whether others have sought to copy Oracea®, the commercial embodiment of the Chang patents. *See Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 496 (D. Del. 2006), *aff'd*, 501 F.3d 1263, 1269 (Fed. Cir. 2007) (finding the "copying of others . . . particularly telling" where a racemic form of the innovator drug was unpatented and available as a generic drug and yet generic drug manufacturers sought approval to market a generic version of the innovator drug); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008).

IV. RELIEF AGAINST AMNEAL

67. Whether Plaintiffs are entitled to a permanent injunction restraining and enjoining Amneal (and all persons in active concert with Amneal) from engaging in the commercial manufacture, use, offer for sale, or sale of Amneal's Generic Product within the United States, or importation into the United States, during the term of the Chang '532 patent.

68. Whether Plaintiffs are entitled to a permanent injunction restraining and enjoining Amneal (and all persons in active concert with Amneal) from engaging in the commercial manufacture, use, offer for sale, or sale of Amneal's Generic Product within the United States, or importation into the United States, during the term of the Chang '740 patent.

69. Whether Plaintiffs are entitled to an order pursuant to 35 U.S.C. § 271(e)(4)(A) that the U.S. Food and Drug Administration ("FDA") shall not approve Amneal's Generic Product prior to the expiration date of the Chang '532 patent, or any extension of that date.

70. Whether Plaintiffs are entitled to an order pursuant to 35 U.S.C. § 271(e)(4)(A) that the FDA shall not approve Amneal's Generic Product prior to the expiration date of the Chang '740 patent, or any extension of that date.

EXHIBIT 5

EXHIBIT 5

AMNEAL'S STATEMENT OF ISSUES OF LAW

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TABLE OF AUTHORITIES

Cases

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Other Authorities

Amneal submits the following statement of the issues of law that it contends remain to be litigated, and a citation of authorities relied upon. To the extent any issue of law is deemed to be an issue of fact, it should be so considered. Amneal reserves the right to revise this statement in light of the court's rulings and in light of Galderma's issues of law and fact to be litigated.

I. Noninfringement

A. Legal Standard – Infringement

1. Whether Galderma has proven by a preponderance of the evidence any infringement, either direct or indirect, of any asserted claim of the '532 and '740 patents.

Citation of Authorities

Patent infringement is making, using, importing, offering to sell, or selling a patented invention during the term of the patent without authority. 35 U.S.C. § 271(a). The patentee bears the burden of proving, by a preponderance of the evidence, that the accused product infringes the asserted claims of the patents-in-suit. *Centricut, LLC v. The Esab Group, Inc.*, 390 F.3d 1361, 1367 (Fed. Cir. 2004).

The determination of patent infringement involves a two-step analysis. "The court must first interpret the claims to determine their scope and meaning. It must then compare the properly construed claims to the allegedly infringing device." *PSC Computer Prods., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1357 (Fed. Cir. 2004) (internal citation omitted). Words of a claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The burden of proof resides with the patent owner to establish that each and every claim limitation is present either literally (*i.e.*, identical correspondence), or under the doctrine of equivalents, in the accused product. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S 17, 29 (1997). If any one limitation of the asserted claims is not present in the accused

product, the accused infringing party is entitled to a judgment of noninfringement. *See Laitram Corp. v. Rexnord, Inc*., 939 F.2d 1533, 1535 (Fed. Cir. 1991) ("[T]he failure to meet a single limitation is sufficient to negate infringement of the claim.").

B. Literal Infringement

2. Whether Galderma has proven by a preponderance of the evidence that Amneal's ANDA product literally infringes any asserted claim of the '532 and '740 patents.

Citation of Authorities

"To prove [patent] infringement, the patentee must show that the accused device meets each claim limitation, either literally or under the doctrine of equivalents." *PSC Computer Prods.*, 355 F.3d at 1357. Literal infringement requires the presence of each limitation, exactly as written in the claim. *See DeMarini Sports, Inc. v. Worth, Inc.*, 239 F.3d 1314, 1331 (Fed. Cir. 2001) ("Literal infringement of a claim occurs when every limitation recited in the claim appears in the accused device, *i.e.*, 'when the properly construed claim reads on the accused device exactly.'" (citation omitted)). Scientific theories utilized to establish infringement must demonstrate the presence of all of the limitations recited in the claim. *See Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423 (Fed. Cir. 1994). Scientific tests that are only inferentially relevant to the claims do not meet the standards required for establishing infringement. *Id.*

C. Infringement under the Doctrine of Equivalents

3. Whether Galderma has proven by a preponderance of the evidence that Amneal's ANDA product infringes any asserted claim of the '532 or '740 patents under the doctrine of equivalents.

4. What range of equivalents, if any, Galderma is entitled to, and whether the alleged equivalent performs the same function in the same way with the same result as the asserted claim element(s).

Citation of Authorities

If no literal infringement is found, the accused product or process may still be found to infringe under the doctrine of equivalents but only if the difference between the claim term that is not literally found and the corresponding element in the accused product or process is "insubstantial." *Warner-Jenkinson Co. v. Hilton David Chem. Co.*, 520 U.S. 17, 39-40 (1997). In every case where no literal infringement is found, the trial judge must ensure that infringement under the doctrine of equivalents is considered. *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1522 (Fed. Cir. 1995).

A generalized showing of equivalency between the invention as a whole and the allegedly infringing product or process is not sufficient to show infringement; rather, infringement analysis under the doctrine of equivalents proceeds element-by-element. *See Warner–Jenkinson*, 520 U.S. 17, 29 (1997) ("the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole"). The Federal Circuit recognizes that "primary test for equivalency is the 'function-way-result' . . . whereby the patentee may show an equivalent when the accused product or process performs substantially the same function, in substantially the same way, to achieve substantially the same result, as disclosed in the claim." *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1296 (Fed. Cir. 2009). As "all three prongs of the function-way-result test must be satisfied to establish infringement under the doctrine of equivalents, the absence of any one prong is dispositive." *Al-Site Corp. v. Bonneau Co.*, 22 F.3d 1107 (Fed. Cir. 1994).

The patentee must provide "particularized testimony and linking argument" as to the 'insubstantiality of differences' [between the claim and the accused product] or with respect to the function-way-result test. *Amgen Inc. v. F. Hoffman-LA Roche Ltd.*, 580 F.3d 1340, 1382 (Fed. Cir. 2009) (*citing Texas Instruments Inc. v. Cypress Semiconductor Corp*., 90 F.3d 1558, 1567 (Fed. Cir. 1996)). Such evidence must be presented on a limitation-by-limitation basis and not based on the invention as a whole. *Id*.

Bioequivalency may be relevant to the function prong of the function-way-result test, but courts consider bioequivalency and equivalent infringement as different inquiries. *Abbott Labs.* 566 F.3d at 1298 (Fed. Cir. 2009). The Federal Circuit has clarified that "[b]ioequivalency is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes. In contrast, equivalency for purposes of patent infringement requires an element-by-element comparison of the patent claim and the accused product, requiring not only equivalent function but also equivalent way and result. Different attributes of a given product may thus be relevant to bioequivalency but not equivalent infringement, and vice versa." *Id*.

Bioequivalency is "potentially relevant" to the question of infringement in certain circumstances. *Abbott Labs v, TorPharm, Inc.*, 300 F.3d 1367, 1374 n.2 (Fed. Cir. 2002) (stating that if a generic product reports pharmacokinetic data on its label that falls within the asserted patent claim, the label can be used to support a finding of infringement). However, bioequivalency on its own is not sufficient to establish infringement. *Abbott Labs v. Sandoz*, 566 F.3d 1282, 1298 (Fed. Cir. 2009).

D. Contributory and Induced Infringement

5. Whether Galderma has proven by a preponderance of the evidence that Amneal induced any infringement of the '532 and '740 patents.

6. Whether Galderma has proven by a preponderance of the evidence that Amneal contributed to any infringement of the '532 and '740 patents.

Citation of Authorities

Section 271(c) prohibits the sale of a product that can be used in a patented method if the product is "not a staple article or commodity of commerce suitable for substantial noninfringing use." 35 U.S.C. 271 (c) (2012). Contributory infringement requires proof of direct infringement and also requires that the accused product have "no use except through practice of the patented method." *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1374 (Fed. Cir. 2003); *accord Sony Corp. of Am. v. Universal City Studios, Inc.*, 464 U.S. 417 (1984) (same).

Section 271(b) provides: "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. 271(b) (2012). Like contributory infringement, the burden of proving induced infringement is heavy. "In order to prevail on an inducement claim, the patentee must establish first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *ACCO Brands, Inc. v. ABA Locks Mfr. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007) (quotations and citation omitted); *see also Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990). "[I]nducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Med Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc) (*citing Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd*, 125 S. Ct. 2764, 2780 (2005); *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990)).

II. Patent Invalidity

A. Anticipation

7. Whether one or more of the asserted claims of the '532 or '740 patents is invalid as anticipated pursuant to 35 U.S.C. § 102.

Citation of Authorities

A claim is anticipated when a prior art reference discloses every claim limitation, either explicitly or inherently. *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). A claim is inherently anticipated if the prior art necessarily functions in accordance with or includes the claimed limitations. *Id*; *see also Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ([A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.). "Inherency is not necessarily coterminous with knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art." *Id*; *see also Schering* 339 F.3d at 1377 (rejecting the contention that inherent anticipation requires recognition in the prior art).

Patents asserted as prior art in an invalidity defense are presumed enabled. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. *Id.* at 1355. However, the Federal Circuit held that a presumption arises that *both* the claimed and unclaimed disclosures in a prior art patent are enabled. *Id.* (emphasis added). It is then the burden of the patentee to prove that the relevant claimed or unclaimed disclosures of the prior art patent are not enabled and therefore not pertinent prior art. *Id*; *see also Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1337 (Fed. Cir. 2013) ("Because we must presume a patent enabled, the challenger bears the burden, throughout the litigation, of proving

lack of enablement by clear and convincing evidence."). Further, "[t]he anticipation analysis asks solely whether the prior art reference discloses and enables the claimed invention, and not how the prior art characterizes that disclosure or whether alternatives are also disclosed." *Hewlett-Packard Co. v. Mustek Sys., Inc.* 340 F.3d 1314, 1325 (Fed. Cir. 2003).

In order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation. *Finisar Corp. v.* DirecTV *Group, Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008) (*citing In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1379 (Fed. Cir. 2007)). The "undue experimentation" component of that equation examines (1) the quantity of experimentation; (2) the amount of direction or guidance present; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

"All the disclosures in a [prior art] reference must be evaluated, including nonpreferred embodiments, . . . and a reference is not limited to the disclosure of specific working examples." *In re Mills*, 470 F.2d 649, 651 (C.C.P.A. 1972). Likewise, "anticipation does not require actual performance of suggestions in a disclosure…anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001) (*citing In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) ("It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.")); *see also SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344 (Fed. Cir. 2005) (holding a patent invalid for anticipation based on the prior art that disclosed a method for the production of the drug even though the drug was not

actually made, saying that "whether it was actually possible to make pure PCH anhydrate before the critical date of the '723 patent is irrelevant" because the process was disclosed in an enabling manner).

This court, too, has found that a prior art reference to be anticipating even though the reference did not actually produce a specific example of the composition in question. *Gen. Elec. Co. v. Hoechst Celanese Corp*., 740 F.Supp. 305, 316 (D. Del. 1990) (holding prior art reference disclosed both the product and the process necessary to make claimed composition and that prior art "need not actually exemplify [the claimed] composition to anticipate under section 102(b)").

Invalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation. *See Atlas Powder Co. v. Ireco Inc*., 190 F.3d 1342, 1347 (Fed. Cir. 1999). However, material not explicitly contained in the single, prior art document may still be considered for purposes of anticipation if that material is incorporated by reference into the document. *See Ultradent Prods., Inc. v. Life–Like Cosmetics, Inc.*, 127 F.3d 1065, 1069, 1339–40 (Fed. Cir. 1997) (holding material incorporated by reference into a document may be considered in an anticipation determination.).

Under 35 U.S.C. § 102(d), a patent or patent application is considered prior art to a claimed invention and is considered to have been effectively filed, with respect to any subject matter described in the patent or application--

> (1) if paragraph (2) does not apply, as of the actual filing date of the patent or the application for patent; or
>
> (2) (2) if the patent or application for patent is entitled to claim a right of priority under section 119, 365(a), or 365(b), or to claim the benefit of an earlier filing date under section 120, 121, or 365(c), based upon 1 or more prior filed

> applications for patent, as of the filing date of the earliest such application that describes the subject matter.

A patent application includes the full disclosure of a prior patent application when it is incorporated by reference in its entirety. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1283 (Fed. Cir. 2000). Whether and to what extent a patent application incorporates material by reference is a question of law. *Harari v. Hollmer*, 602 F.3d 1351, 1351 (Fed. Cir. 2010). The applicable standard in making that determination is whether one reasonably skilled in the art would understand the application as describing with sufficient particularity the material to be incorporated. *Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378–79 (Fed. Cir. 2007). The use of the phrase "hereby incorporated by reference" constitutes "broad and unequivocal language" incorporating a document by reference. *Harari v. Lee*, 656 F.3d 1331, 1335 (Fed. Cir. 2011) (holding phrase "[t]he disclosures of the two applications are hereby incorporate[d] by reference" incorporated the entire previous patent application into the current one).

Further, a nonprovisional application should be treated "as though filed on the date of its corresponding provisional application" so long as the provisional application provides written support for the claimed invention. *In re Giacomini*, 612 F.3d 1380, 1383 (Fed. Cir. 2010).

When the prior art includes a patent owned by the patentee, the claims of the prior patent merit special attention to what they disclose and do not disclose because they will often reflect the patentee's own view of the ordinary skill in the art at the time the patent was filed. *Abbott Labs. v. Andrx Pharm., Inc.*, 452 F.3d 1331, 1341 (Fed. Cir. 2006). "[A] presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Id.* (quoting *Amgen Inc.*, v. *Hoechst Marion Roussel, Inc*. 314 F.3d 1313, 1355 (Fed. Cir. 2003)). Courts presume that filed claims satisfy the written description and enablement requirements of 35 U.S.C. § 112.

Id. In *Abbott Labs*, the court concluded that when the patentee prosecuted its prior art, it made certain representations to the PTO and the public concerning the scope of its claims, and both the claimed and unclaimed disclosures were enabled. *Id*. Consequently, the patentee cannot later challenge the enablement of its own prior art patent by arguing that there wasn't sufficient disclosure of certain embodiments when it represented to the PTO that those disclosures were enabled. *Id.*

Prior art can anticipate a claim when its disclosed range entirely encompasses and does not significantly deviate from a patentee's claimed ranges. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005) (holding prior art disclosed and anticipated claimed "effective amount" ranges where claims recited a number of different ranges that were entirely encompassed by, and did not significantly deviate from, the patentee's claimed ranges). One ingredient can anticipate even though it appears without special emphasis in a longer list [in the prior art]. *Id.* at 1376. "[T]he disclosure is prior art to the extent of its enabling disclosure." *Id.*; *see also Atlas Powder Co. v. Ireco, Inc*., 190 F.3d 1342, 1349 (Fed. Cir. 1999) (finding prior art disclosure of 33-80% solid ammonium nitrate composition anticipated a disclosure of 60-90%).

"[W]hen a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim." *Atlas Powder Co,* 190 F.3d at 1346. Whether an earlier disclosed genus may, in certain circumstances, anticipate a later species is an inquiry that necessarily includes a factual component. *OSRAM Sylvania, Inc. v. Am. Induction Techns., Inc*., 701 F.3d 698, 705 (Fed. Cir. 2012). Key facts that the Federal Circuit has analyzed when determining if a genus disclosure of a range can anticipate a narrower range include whether there are no considerable differences between the broader range and the narrower range and whether the narrower range is critical. *ClearValue, Inc. v.*

Pearl River Polymers, Inc., 668 F.3d 1340, 1345 (Fed. Cir. 2012). In *ClearValue*, the court held that a claim directed to "[a] process for clarification of water of raw alkalinity less than or equal to 50 ppm" was anticipated by prior art that disclosed a process for clarifying water with alkalinity of 150 ppm or less. *Id.* In so holding, the court reasoned that the prior art range was not too broad to anticipate because there was no evidence that the 50 ppm limitation was critical or that the claimed method would work differently at different points within the prior art range of 150 ppm or less. *Id.*

The Federal Circuit has also upheld a finding of inherent anticipation where the board relied upon its own calculations and inferences to conclude that the limitation was inherently disclosed. *In re Gately*, 69 F. App'x 993, 995 (Fed. Cir. 2003) (affirming anticipation by inherency rejection based solely on Board's own calculations and inferences and "some assumptions, judgments, and even conjectures").

B. Obviousness

1. Prima Facie Showing

8. Whether one or more of the asserted claims of the '532 and '740 patents are invalid due to obviousness pursuant to 35 U.S.C. § 103.

Citation of Authorities

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. Obviousness is a question of law based on four underlying factual determinations: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level or ordinary skill in the pertinent art; and (4) secondary considerations, if any, of nonobviousness. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398,

406-407 (2007) (*citing Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003) (*citing Graham*, 383 U.S. at 17-18).

Obviousness is a "question of law based on underlying findings of fact." *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). Among those facts include: [w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references." *In re Fulton*, 1391 F.3d 1195, 1199-200 (Fed. Cir. 2004). In determining obviousness, courts must look at the prior art **as a whole** to see if there is a "suggest[ion] [of] the desirability" of the combination. *In re Beattie*, 974 F.2d 1309, 1311 (Fed. Cir. 1992) (internal quotation omitted) (emphasis added). Further, when determining the scope and content of the prior art, a prior patent must be considered in its entirety. *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, (Fed. Cir. 1983).

"Under § 103 . . . a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

Obviousness is judged under an expansive and flexible approach driven by common sense, and thus, patentability requires "more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417. This flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 419.

Other forces, such as market demand, also may be examined to determine whether it would be obvious to combine more than one known element. *Id.* at 418-20. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options

within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under §103." *Id*. at 422. However, only a reasonable expectation of success, not a guarantee, is needed. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). "Common sense teaches . . . that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *KSR*, 550 U.S. at 420.

A prior art reference disclosing a range encompassing a narrower claimed range can establish a prima facie case of obviousness, thereby shifting the burden to the applicant to show that his invention would not have been obvious. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). However, to rebut the prima facie showing the applicant must show that the claimed range is critical. *In re Geisler*, 116 F.3d 1465, 1469-1470 (Fed. Cir. 1997). "When an applicant seeks to overcome a prima facie case of obviousness by showing improved performance in a range that is within or overlaps with a range disclosed in the prior art, the applicant must 'show that the [claimed] range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.'" *Id.* (*quoting In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (emphasis in original)).

A presumption of obviousness is found where a claimed range overlaps with a range disclosed in the prior art. *Ormco Corp. v. Align Tech., Inc*., 463 F.3d 1299, 1311 (Fed. Cir. 2006); *see also Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997). The patentee can rebut that presumption by showing that the prior art teaches away from the claimed range or the claimed

range produces new and unexpected results. *Id. See also Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1577 n. 3 (Fed. Cir. 1993) ("[W]hen the difference between the claimed invention and the prior art is the range or value of a particular variable, then a prima facie rejection is properly established when the difference in range or value is minor.") (emphasis omitted); *In re Malagari*, 499 F.2d 1297, 1303 (C.C.P.A. 1974) (affirming obviousness rejection of claim reciting range of 0.3% to 0.07% over prior art disclosing 0.02% to 0.03% range because applicant failed to show unexpected results or teaching away)).

The fact that a prior art patent discloses many effective combinations does not render any particular formulation less obvious, particularly when each of those prior art combinations are used for the identical purpose as the claimed invention. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989); *see In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among 'thousands' of compounds"); *see also In re Susi*, 440 F.2d 442, 445 (C.C.P.A. 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellant's generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives").

Further, the mere absence from the prior art of a teaching or a limitation recited in the patent at issue is insufficient for a conclusion of nonobviousness. *Merck & Co.*, 874 F.2d at 807. The court found that a determination of obviousness was not precluded simply because the prior art did not "teach the specific ratios of the combinations" disclosed in the patent at issue. *Id.* "Unlike a section 102 defense which requires that a single reference describe each and every element of a claimed invention, 'the question under 35 USC 103 is not merely what the

references expressly teach but what they would have suggested to one of ordinary skill in the art at the time the invention was made.'" *Id*. (*quoting In re Lamberti,* 545 F.2d 747, 750 (C.C.P.A. 1976) (finding that obviousness can still be found when the prior art suggests but does not teach the combinations claimed in the patent at issue)).

A reference does not teach away if it merely expresses a general preference for an alternative invention but does not "criticize, discredit, or otherwise discourage" investigation into the invention claimed. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). In fact, the Federal Circuit has said that in order to find that a prior art reference teaches away from a disclosed embodiment, it must provide clear discouragement from using a particular combination as opposed to a mere preference for another embodiment. *Syntex (U.S.A.) LLC v. Apotex, Inc*., 407 F.3d 1371, 1380 (Fed. Cir. 2005) ("A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination").

2. Objective Indicia of Nonobviousness ("Secondary Considerations")

9. Whether Galderma has shown that any secondary considerations overcome a prima facie showing of obviousness.

Citation of Authorities

Objective evidence of nonobviousness must be considered in an assessment of obviousness. *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 903 (S.D. Ind. 2005) *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006). "Such objective evidence, when present, must be considered and includes the extent of commercial success of the patented invention, unexpected properties of the invention compared to the prior art, whether the invention satisfies a long-felt need, whether others have failed to find a solution to the problem plaguing the art, and any copying of the invention by others." *Id.* To establish secondary considerations of nonobviousness, argument and conjecture are insufficient. *Demaco Corp. v. F. Von Langsdorff*

Licensing Ltd., 851 F.2d 1387, 1393 (Fed. Cir. 1988). "These legal inferences or subtests … focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible of judicial treatment than are highly technical facts often present in patent litigation." *Graham v. John Deere Co.*, 383 U.S. 1, 35-36 (1966). To provide proper evidence of secondary considerations, a patentee must establish a nexus between the evidence presented and the merits of the claimed invention. *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). The patentee bears the burden of demonstrating such "a legally and factually sufficient connection." *In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

Even when supported by substantial evidence, secondary considerations are often insufficient to overcome a prima facie case of obviousness. *KSR*, 550 U.S. 398 at 427 (2007) ("Where, as here, the content of the prior art, the scope of the patent claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate."); *see also Ball Aerosol & Specialty Container, Inc. v. Ltd. Brands, Inc.*, 555 F.3d 984, 994 (Fed. Cir. 2009) (finding indications of commercial success not to outweigh "clear indication of obviousness apparent from the prior art"); *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (affirming this court's finding of obviousness based on the strong prima facie showing of obviousness despite "substantial evidence" of secondary considerations); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) ("Moreover, as we have often held, evidence of secondary considerations does not always overcome a strong prima facie showing of obviousness."); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) (finding that Pfizer's alleged unexpectedly superior results were insufficient to overcome a strong case of obviousness).

(a) Unexpected Results

10. Whether the claimed inventions produced new and unexpected results.

Citation of Authorities

"[B]y definition, any superior property must be *unexpected* to be considered as evidence of nonobviousness." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (emphasis in original). "[I]n order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected." *Id*. (explaining that [t]he fact that amlodipidine besylate was the best of the seven acid addition salts actually tested provides nothing more than routine optimization that would have been obvious to one of ordinary skill in the art.")

Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Further, an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). Similarly, "[a]n applicant cannot prove unexpected results with attorney argument and bare statements without objective evidentiary support." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

(b) Long-felt Need

11. Whether a long-felt need existed for the claimed inventions, and if so, whether the claimed inventions satisfied such a need.

Citation to Authority

A long-felt but unsolved need is another secondary consideration of non-obviousness. *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010). Courts have rejected the patentee's evidence of long-felt need when the differences between the

prior art and claim invention were small and evidence showed that other prior art devices met the alleged need. *Id.* The patentee must show that the material difference between the prior art and the invention satisfied the long-felt and unmet need. *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (finding, while the evidence showed that the overall invention drew praise, there was no evidence that the success of the patent's commercial embodiment was attributable to the only material difference between the invention and the prior art).

The long-felt need should be a need created by inadequacies in the technical knowledge, not one due to business-driven market forces that are unrelated to technical considerations. *Friskit, Inc. v. Real Networks, Inc.*, 306 F. App'x 610 (Fed. Cir. 2009) (rejecting the patentee's long-felt need argument because none of the patentee's evidence suggested that its approach presented any technical challenge to one of ordinary skill in the art once market forces had created a demand for the innovation). The key question is whether one of ordinary skill in the art would have been motivated to combine the references. "[T]he fact that two disclosed apparatus would not be combined by businessmen for economic reasons is not the same as saying that it could not be done because skilled persons in the art felt that there was some technological incompatibility that prevented their combination. Only the latter fact is telling on the issue of nonobviousness." *Orthopedic Equip. Co., Inc. v. U.S.*, 702 F.2d 1005, 1013 (Fed. Cir. 1983).

Evidence of a long-felt need requires more than uncorroborated expert testimony. The Federal Circuit has held that bare assertions made by an expert with no supporting data is not evidence of long-felt need. *See Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1333 (Fed. Cir. 2009). Additionally, if analogous prior art was already effective for solving the problem claimed to be solved by a patent at issue, there can be no long-felt need to such

problem. *Electro Scientific Indus., Inc. v. Gen. Scanning Inc*., 247 F.3d 1341, 1352 (Fed. Cir. 2001).

(c) Failure of Others to Make the Invention

12. Whether others skilled in the art of the claimed inventions tried and failed to make the claimed inventions.

Citation to Authorities

The patentee must establish that others skilled in the art tried and failed to find a solution for the problem solved by the inventor. *See Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1540 (Fed. Cir. 1983). Merely citing references where others have investigated the problem and its cause but did not explore a solution is insufficient evidence to overcome a finding of obviousness. *Id*. Like other secondary considerations, any alleged "failure of others" must be tied to the claims and the patentee must show that others failed because their attempts lacked the features. *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006) ("Again, the evidence does not suggest that these prior attempts failed because the devices lacked the claimed features.").

Pointing to abandoned efforts at making a claimed innovation is not sufficient to support an inference of nonobviousness. *See Kimberly-Clark Worldwide, Inc. v. First Quality Baby Products, LLC,* 900 F. Supp. 2d 903 (E.D. Wis. 2012) (noting that such evidence merely shows that a party considered and then canceled its project, not that it failed on technical merits). Particularly, a calculated business judgment not to continue is not a failed attempt by others. *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co*., 464 F.3d 1356, 1371-72 (Fed. Cir. 2006). In *Dystar*, the court refused to find "failure of others" where a company decided not to pursue and invention "because it would involve increased shipping costs, might require customers to invest in additional storage facilities, and would cost more to produce,

likely forcing it to increase prices to customers." *Id.* "[The company's] decision was thus not a failed attempt, but a calculated business judgment to abandon a potential new product line."

(d) Copying

13. Whether Amneal's alleged copying of the patented inventions is objective evidence of non-obviousness.

Citation of Authorities

"[A] showing of copying is not compelling evidence of non-obviousness in Hatch-Waxman cases due to the nature of the ANDA process." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 458 (D. Del. 2010) (find that alleged infringer's reverse engineering was not persuasive objective evidence of non-obviousness); *see also Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 373-74 (D. Del. 2009). Any copying in the ANDA context, rather than due to nonobviousness, is due to "the ANDA procedures established by the Hatch-Waxman Act [that] require[] generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, No. IP 00-38-C H/K, 2001 WL 1397304, at *14 (S.D. Ind., Oct. 29, 2001). *See also Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, IP 02-0512-C-B/S, 2004 WL 1724632 (S.D. Ind. July 29, 2004) aff'd, 05-1044, 2005 WL 1635262 (Fed. Cir. July 13, 2005) ("because the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects, Teva's demonstration of equivalency of Sarafem to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention.").

(e) Commercial Success

14. Whether there is a nexus between the claimed inventions and any alleged commercial success.

Citation of Authorities

Evidence of commercial success is only relevant if there is a nexus between the invention and the commercial success. *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). The party submitting the evidence of commercial success must show "that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re DBC*, 545 F.3d 1373, 1384 (Fed. Cir. 2008) (*citing In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)). "Furthermore, the asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). The alleged infringer may rebut evidence of a nexus by showing that it is "due to an unclaimed feature of the device" or "if the feature that creates the commercial success was known in the prior art." *Ormco*, 463 F.3d at 1312. In these cases the commercial success of the product is irrelevant and fails to raise any doubt as to the obviousness of the claimed invention. *Id. See also In re Huai-Hung Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) ("[I]f it is not established that the claimed and novel range for a controlled release oxymorphone formulation causes commercial success where the prior art range would not, then it will be difficult to show the required nexus.").

In cases involving pharmaceutical products, the patentee must also demonstrate that the undisputed commercial success is a result of the "drug's superior properties, as opposed to other factors such as marketing, discounting, and offering incentives to buyers." *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 532 F. Supp. 2d 666, 680 (D.N.J. 2007) *aff'd*, 566 F.3d 999 (Fed. Cir. 2009). Furthermore, where the patentee has a right to exclude others under conditions particular to the Hatch-Waxman framework, the "inference of non-obviousness of [the claimed invention],

from evidence of commercial success, is weak." *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (noting that pioneer drug manufacturer's sales were of little significance because FDA restrictions and other patents precluded market entry by others).

Courts have determined that commercial success can be of minimal probative value on the issue of obviousness when considering the applicability of other patents to a product. *Id.*at 1376. "Financial success is not significantly probative of [whether the claimed invention was non-obvious in light of prior art] in this case because others were legally barred from commercially testing the [relevant] ideas" by other patents claiming elements of the product. *Id.* at 1377. This court reached a similar conclusion in *Senju Pharmaceuticals Co. v. Apotex, Inc.*, finding that evidence of the commercial success of "ZYMAR®, the undisputed commercial embodiment of the '045 patent" was of only "minimal probative value," in light of the fact that "others were legally barred from testing gatifloxacin products until the pediatric exclusivity associated with [a different] patent expires." 717 F. Supp. 2d 404, 426 (D. Del. 2010).

III. Patent Unenforceability

A. Inequitable Conduct

15. Whether, as a matter of law, the '532 and '740 patents are unenforceable due to inequitable conduct.

Citation of Authorities

"Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of a patent." *Therasense, Inv. v. Becton, Dickinson and Co.*, 649 F.3d 1276, 1285 (Fed. Cir. 2011) (en banc). "To prevail on the defense of inequitable conduct, the accused infringer must prove that the applicant misrepresented or omitted material information with the specific intent to deceive the PTO. The accused infringer must prove both elements—intent and materiality—by clear and convincing evidence." *Id.* (*citing Star Scientific Inc. v. R.J. Reynolds*

Tobacco Co., 537 F.3d 1357, 1365 (Fed. Cir. 2008). "Inequitable conduct in the process of procuring a patent taints the property right itself." *Aptix Corp. v. Quickturn Design Sys., Inc.*, 269 F.3d 1369, 1376 (Fed. Cir. 2001). Once inequitable conduct is found, "courts declare the patent unenforceable because the property right is tainted *ab initio*." *Id.* Moreover, even if inequitable conduct only directly concerns one of the claims, it is fatal to the entire patent. *Id.* at 1382.

In a case involving failure to disclose information, the accused infringer must prove that the applicant "knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Therasense*, 649 F.3d at 1290. "Intent and materiality are separate requirements." *Id.* To prove intent, "the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence." *Id.* (quoting *Star*, 537 F.3d at 1366). However, "a district court may infer intent from indirect and circumstantial evidence." *Id.* The facts and circumstances surrounding the questioned activity may also lead to finding of the requisite intent. *Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1190 (Fed. Cir. 1993). Selectively withholding material information is indicative of an intent to deceive for the purposes of inequitable conduct. *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1335 (Fed. Cir. 2012).

Materiality can be established in two ways: but-for materiality or affirmative egregious misconduct. *Therasense*, 649 F.3d at 1292. But-for materiality is established "[w]hen an applicant fails to disclose prior art to the PTO, [and] that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed art." *Id.* at 1291. The egregious misconduct test, on the other hand, gives courts sufficient flexibility to capture extraordinary circumstances that would show materiality. *Id.* at 1293. "When the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false

affidavit, the misconduct is material." *Id.*at 1292. The materiality is shown because "a patentee is unlikely to go to great lengths to deceive the PTO with a falsehood unless it believes that the falsehood will affect issuance of the patent." *Id*. However, egregious misconduct is not limited solely to filing false affidavits. *Id.* at 1293. The Federal Circuit said that this "approach [is] sensitive to varied facts and equitable considerations, [and] it is also consistent with the early unclean hands cases—all of which dealt with egregious misconduct. *Id.* The affirmative act of intentionally removing data and presenting incomplete information to the PTO is "particularly egregious because, unlike [an] applicant's failure to disclose, for example, a material patent reference, the examiner has no way of securing the [removed data] on his own." *Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1193 (Fed. Cir. 1993).

A patent is invalid due to inequitable conduct when patentee's counsel knowingly witholds valuable information from the PTO during prosecution of the patent. *Worldwide Home Products, Inc. v. Time Inc*., No. 11-cv-03633-LTS-MHD (S.D.N.Y. Sept. 20, 2013). In *Worldwide*, the prosecuting patent attorney did not disclose to the PTO either the physical prior art that he had in his possession or the high-resolution photographs of the art, both far clearer demonstrations of the features of the art than the low-resolution thumbnail images that were actually provided to the examiner. *Id* at *3, *16. The attorney claimed that he provided the low-resolution reference pictures "out of an abundance of caution" even though he did not know whether they were prior art. *Id.* at *16. The court, however, found that the attorney knew the reference was material and had the same features as the patent in question after a telephone interview with the examiner, where he drew a false distinction between the plaintiff's device and the prior art reference. *Id.* at *14-15. The court determined that these actions proved that the attorney selectively withheld the most relevant information from the PTO examiner, which was

indicative of a clear intent to deceive. *Id* at *16. Consequently, the court granted the Defendants' motion for summary judgment for noninfringement and declared the patent invalid and unenforceable as the product of inequitable conduct.

The Federal Circuit recently found inequitable conduct based on affirmative egregious misconduct. *Intellect Wireless, Inc. v. HTC Corp*., 2012-1658 Decision, (Fed. Cir. October 9, 2013). In *Intellect Wireless*, to overcome a prior art rejection, the inventor filed a false declaration that the claimed invention was actually reduced to practice [before the prior art]. *Id*. at 3-4. However, the district court found that the invention was never reduced to practice. *Id*. at 4. The inventor then contended that the falsity was corrected when the prosecuting attorney filed a revised declaration that stated the inventor was relying on constructive reduction to practice. *Id*. But the court clarified that when an applicant files a false declaration, he is required to:

> 'expressly advise the PTO of [the misrepresentation's] existence, stating specifically wherein it resides' . . . . Further, 'if the misrepresentation is of one or more facts, the PTO [must] be advised what the actual facts are.' Finally, the applicant must 'take the necessary action openly. It does not suffice that one knowing of misrepresentations in an application or in its prosecution merely supplies the examiner with accurate facts without calling his attention to the untrue or misleading assertions sought to be overcome, leaving him to formulate his own conclusions.'

Id. at 5-6 (*quoting Rohm & Haas Co. v. Crystal Chem.Co*, 722 F.2d 1556, 1572 (Fed. Cir. 1983). The court affirmed the district court's finding of materiality [satisfying inequitable conduct] when the inventor issued a declaration to the PTO containing false statements that was never "actually withdrawn, specifically called to the attention of the PTO or fully corrected." *Id.* (*quoting Intellect Wireless, Inc. v. HTC Corp.*, 910 F. Supp. 2d 1056 (N.D. Ill. 2012)). The Federal Circuit affirmed the district court's holding that the inventor engaged in affirmative egregious misconduct when he filed the false declaration. *Id* at 7. "Given the false statements and the clear failure to do what is necessary according to our precedent to cure the misconduct, the

argument that materiality has not been established is entirely without merit." *Id.* at 8. Likewise upholding the district court's finding of intent to deceive, the Federal Circuit affirmed the district court's judgment that the asserted patents were unenforceable due to inequitable conduct. *Id.* at 11.

Patent prosecution is an *ex parte* process and, consequently, "[p]ublic interest demands that all facts relevant to such matters be submitted formally or informally to the Patent Office, which can then pass upon the sufficiency of the evidence. Only in this way can that agency act to safeguard the public in the first instance against fraudulent patent monopolies." *Precision Instrument Mfg. Co. v. Auto. Maint. Mack Co*., 324 U.S. 806, 816 (1945)). The Supreme Court has adopted the reasoning of the PTO that "the nature of an application for patent, [and] the relationship of attorneys to the Patent Office requires the highest degree of candor and good faith. In its relation to applicants, the [PTO examiner] must rely upon their integrity and deal with them in a spirit of trust and confidence." *Kingsland v. Dorsey*, 338 U.S. 318, 319 (1950) (quoting statement made by the Patent Office Committee on Enrollment and Disbarment) (ellipses and internal quotation marks omitted). This duty of candor is codified in 37 C.F.R. § 1.56(a) as follows:

> Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [PTO examiner], which includes a duty to disclose to the [PTO examiner] all information known to that individual to be material to patentability . . . .

A "[v]iolation of the duty of candor constitutes inequitable conduct." *Avocent Redmond Corp. v. Raritan Americas, Inc*., 921 F. Supp. 2d 229, 242 (S.D.N.Y. 2013). A prior art reference need not invalidate a claim to meet the but-for materiality requirement. *Id.*

B. Breach of Contract

16. Whether Plaintiffs breached the terms of Amneal's Offer of Confidential Access ("OCA") and whether that breach warrants equitable relief.

An OCA accompanying a Paragraph IV Notice Letter may impose "such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information," including, for example, a prosecution bar. 21 U.S.C. § 355(j)(5)(C)(i)(III). The purpose of a patent-prosecution bar is to avoid the risk that a disclosing party's confidential information will be used, inadvertently or otherwise, in connection with patent-prosecution activities. *See In re Deutsche Bank Trust Co. Ams.*, 605 F.3d 1373, 1378-80 (Fed. Cir. 2010). A request for the ANDA is, by statute, "considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract." 21 U.S.C. § 355(j)(5)(C)(i)(III). "It is very difficult for the human mind to compartmentalize and selectively suppress information once learned, no matter how well intentioned the effort may be to do so." *In re Deutsche Bank*, 605 F.3d at 1378.

"[A] legal remedy may be inadequate where a party's injury from breach of contract is either noncompensable or cannot be valued with reasonable certainty." *El Paso Natural Gas Co. v. TransAmerican Natural Gas Corp.*, 669 A.2d 36, 40 (Del. 1995). *Cf. Chavin v. H.H. Rosin & Co.*, Del.Supr., 246 A.2d 921, 922 (1968). The Federal Circuit has granted equitable relief in the form of patent unenforceability even outside of a finding of inequitable conduct. *Qualcomm Inc. v. Broadcom Corp.*, 548 F.3d 1004, 1026 (Fed. Cir. 2008). The court in *Broadcom* upheld a finding of breach of duty to disclose duty to disclose when Qualcomm failed to disclose its

patents to a standards-setting organization. *Id.* at 1008. The court held that "a district court may in appropriate circumstances order patents unenforceable . . . as long as the scope of the district court's unenforceability remedy is properly limited in relation to the underlying breach." *Id.* at 1026.

Under New York law, an allegation of unauthorized disclosure of confidential data will state a breach of contract claim against for breach of a nondisclosure agreement. *Natural Organics, Inc. v. Smith*, 832 N.Y.S. 2d 76 (App. Div. 2d. 2007). To obtain a preliminary injunction to prevent the breach of a confidentiality agreement by restraining the defendant from competing with the plaintiff, the restriction must be temporally and geographically reasonable and necessary to protect the defendant's legitimate business interests. *Delta Enter. Corp. v Cohen*, 940 N.Y.S. 2d 43 (App. Div. 1st. 2012). A plaintiff is entitled to preliminary injunctive relief [as a remedy for breach of a confidentiality agreement] if it can show a probability or likelihood of success on the merits, a danger of irreparable injury without such relief, and a balancing of the equities in its favor. *U.S. Reinsurance Corp. v. Humphreys*, 618 N.Y.S. 2d 270 (App. Div. 1st. 1994) (finding the plaintiff had shown sufficient evidence of probable irreparable harm when defendant disclosed items in research or development after signing a Confidentiality Agreement and granting injunctive relief).

The Delaware Supreme Court recently found "actual"—and irreparable—injury for a party's violation of a non-disclosure agreement with a company that had disclosed non-public information in connection with merger discussions. *Martin Marietta Materials, Inc. v. Vulcan Materials Co.*, 68 A.3d 1208 (Del. 2012). As a remedy, that Court enjoined the breaching party from proceeding with an attempted hostile takeover bid for a four-month period. *Id.* The Delaware supreme court upheld the trial court's finding "that '[the disclosing company] is now

suffering from exactly the same kind of harm" that the non-disclosure agreement sought to prevent; namely, the "improper selective revelation of non-public … information; and that [the disclosing company] suffered a loss of 'negotiating leverage.'" *Martin Marietta Materials, Inc. v. Vulcan Materials Co.*, 68 A.3d 1208, 1227 (Del. 2012) (*quoting Martin Marietta Materials, Inc. v. Vulcan Materials Company*, 56 A.3d 1072, 1144–46 (Del.Ch.2012)).

C. Unclean Hands

17. Whether plaintiffs' unclean hands in breaching the Amneal OCA should bar Plaintiffs' claims of infringement of the '740 patent against Amneal.

Citation of Authorities

The "unclean hands" doctrine applies if "(1) a party seeking affirmative relief (2) is guilty of conduct involving fraud, deceit, unconscionability, or bad faith (3) directly related to the matter in issue (4) that injures the other party and (5) affects the balance of equities between the litigants." *Sun Microsystems, Inc. v. Versata Enterprises, Inc.*, 630 F. Supp. 2d 395, 410 (D. Del. 2009) (*quoting Castle v. Cohen*, 676 F. Supp. 620, 627 (E.D. Pa. 1987)). The matter must have an "immediate and necessary relation to the equity that [the accusing party] seeks." *See Consolidated Aluminum Corp.v. Foseco Int'l Ltd.*, 910 F.2d 804, 810-11 (Fed. Cir. 1990) (*quoting Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933) ("*Keystone I*").

Within certain limits, "courts are free to sanction bad faith conduct that arises during the course of the litigation. These 'inherent powers' to punish bad faith conduct are 'necessarily vested in courts to manage their own affairs so as to achieve the orderly and expeditious disposition of cases.'" *Aptix Corp. v. Quickturn Design Sys., Inc.*, 269 F.3d 1369, 1375 (Fed. Cir. 2001) (*quoting Chambers v. NASCO, Inc.*, 501 U.S. 32, 44 (1991)). Courts have found that a covenant not to sue can be such a sanction. *Par Systems, Inc. v. Iphoton Solutions, LLC*, 4:10-cv-

00393-T (N.D. Tex. Oct. 17, 2012) (granting covenant not to sue as a remedy for an inadvertent violation of a prosecution bar by defendant's counsel).

This court has said that "[t]he clean hands maxim gives broad discretion to the court's equity power in refusing to aid an unclean hands litigant. . . . The court is not bound by any formula, restraint or limitation which restricts the free and just exercise of its equitable discretion. Any willful act, which can rightfully be said to transgress equitable standards, is sufficient." *Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 343 F. Supp. 2d 272, 321 (D. Del. 2004) (internal citations omitted). "The governing principle is 'that whenever a party who, as actor, seeks to set the judicial machinery in motion and obtain some remedy, has violated conscience, or good faith, or other equitable principle, in his prior conduct, then the doors of the court will be shut against him in limine; the court will refuse to interfere on his behalf, to acknowledge his right, or to award him any remedy.'" *Keystone I,* 290 U.S. at 244-245 (*quoting* Pomeroy, Equity Jurisprudence (4th ed.) § 397).

In reference to violations of protective orders, "Fed. R. Civ. P. 37(b) empowers the courts to impose sanctions for failures to obey discovery orders. In addition to a broad range of sanctions, including contempt, Fed. R. Civ. P. 37(b)(2) authorizes the court to impose a concurrent sanction of reasonable expenses, including attorney's fees, caused by the failure to obey a discovery order." *Falstaff Brewing Corp. v. Miller Brewing Co.*, 702 F.2d 770, 784 (9th Cir. 1983). When these breaches [of a protective order] occur under the court's watch, sanctions are wholly appropriate." *Eagle Comtronics, Inc. v. Arrow Commc'n Labs., Inc.*, 305 F.3d 1303, 1314 (Fed. Cir. 2002) (holding a party's use of a competitor's patent application obtained through discovery for purposes unrelated to the litigation violated the protective order and should be sanctioned at the district court's discretion).

In *Keystone I*, evidence was introduced that the patentee knowingly suppressed information about a prior use that was potentially fatal to the asserted patents. *Keystone I*, 290 U.S. at 243-44. Specifically, upon learning of the prior use, the patentee paid the paid the party who engaged in the prior use to suppress that fact. *Id.* As a remedy, the Court affirmed the lower court's decision to dismiss the infringement complaints with prejudice on the affected patents. *Id.* at 244. "It is one of the fundamental principles upon which equity jurisprudence is founded, that before a complainant can have a standing in court he must first show that not only has he a good and meritorious cause of action, but he must come into court with clean hands. He must be frank and fair with the court, nothing about the case under consideration should be guarded, but everything that tends to a full and fair determination of the matters in controversy should be placed before the court." *Keystone I*, 290 U.S. at 244.

Similarly, in *Hazel-Atlas*, the Supreme Court upheld a lower court's dismissal of a patent infringement case based on the patentee's misconduct before the court. *Hazel-Atlas Glass Co. v. Hartford-Empire Co.*, 322 U.S. 238 (1944). There, when faced with "insurmountable Patent Office opposition" to the application that matured as the patent ultimately at issue, the patentee fraudulently hired a consultant to write an industry publication praising the invention with the sole purpose of aiding prosecution. *Id.* at 240-41. The court below, relying extensively on this article, entered judgment of infringement and validity. *Id.* As a remedy, the Court reversed the finding of infringement and validity below, and ordered dismissal of the action with prejudice. *Id.* at 251.

The Federal Circuit likewise affirmed a district court's dismissal of plaintiff's patent-infringement claims due to plaintiff's "unclean hands" when the patent-owner/inventor fabricated a false conception date for his invention during litigation. *Aptix Corp. v. Quickturn*

Design Sys., Inc., 269 F.3d 1369 (Fed. Cir. 2001). The trial court determined "that the defendant had attempted 'to defraud the Court and to strengthen its patent through a premeditated and sustained campaign of lies and forgery.'" *Id.* at 1373 (*quoting Aptix Corp. v. Quickturn Design Sys.*, 2000 WL 852813, at *23 (N.D. Cal. June 14, 2000)). Consequently, Federal Circuit affirmed the trial court's decision to dismiss the infringement complaint due to the plaintiff's unclean hands. *Id.* at 1374.

IV. Permanent Injunction

The Supreme Court has defined the factors involved when determining equitable relief, saying that "[a]ccording to well-established principles of equity, a plaintiff seeking a permanent injunction must satisfy a four-factor test before a court may grant such relief. A plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction. *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006). Further, the Court held that "[t]hese familiar principles apply with equal force to disputes arising under the Patent Act. . . . [T]he Patent Act expressly provides that injunctions 'may' issue 'in accordance with the principles of equity.'" *Id.* at 391-392 (*quoting* 35 U.S.C. § 283 (2006) (providing that, "[t]he several courts having jurisdiction of cases under this title may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable.").

However, those requesting equitable relief must come to court with clean hands in order to be afforded such a remedy. "It is one of the fundamental principles upon which equity jurisprudence is founded, that before a complainant can have a standing in court he must first

show that not only has he a good and meritorious cause of action, but he must come into court with clean hands. He must be frank and fair with the court, nothing about the case under consideration should be guarded, but everything that tends to a full and fair determination of the matters in controversy should be placed before the court." *Keystone I*, 290 U.S. at 244 (*quoting Story's Equity Jurisprudence* (14th Ed.) § 98).

EXHIBIT 6

EXHIBIT 6 OF PROPOSED JOINT PRETRIAL ORDER
WITNESSES PLAINTIFFS INTEND TO CALL IN PERSON
OR BY PRIOR SWORN TESTIMONY

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES INC., GALDERMA LABORATORIES, L.P. and SUPERNUS PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 11-1106 (LPS)
AMNEAL PHARMACEUTICALS, LLC. and AMNEAL PHARMACEUTICALS CO. (I) PVT. LTD.,	)	
Defendants.	)	

WITNESSES PLAINTIFFS INTEND TO CALL
IN PERSON OR BY PRIOR SWORN TESTIMONY

Plaintiffs intend to call the following witnesses in person in their case-in-chief or in rebuttal during the upcoming trial. To the extent permitted by the Federal Rules of Evidence, Plaintiffs also reserve the right to introduce prior sworn testimony (*e.g.*, deposition testimony) of any witness named below.

1. Henry G. Grabowski
2. Edward M. Rudnic, Ph.D.
3. Guy F. Webster, M.D., Ph.D.

Plaintiffs may call the following witnesses in person in their case-in-chief or in rebuttal during the upcoming trial. To the extent permitted by the Federal Rules of Evidence, Plaintiffs also reserve the right to introduce prior sworn testimony (*e.g.*, deposition testimony) of any witness named below.

1. Padmanabh Bhatt
2. Paul M. Clark
3. Brian M. Johnson

In addition, Plaintiffs may introduce the deposition testimony of one or more of the following fact or Rule 30(b)(6) witnesses, or call them live if available and if time permits:

1. Payal Bhaiya
2. Jones W. Bryan, Jr.
3. Richard Chang
4. Donald M. Eades
5. Candis Edwards
6. Ravikumar Nithiyanandam
7. Mary Elisa Lane

8. Narasimhan Mani

9. Nikunj Patel

10. Arash Raoufinia

11. Niraj Shah

Plaintiffs reserve the right to call any additional witnesses necessitated by any of the Court's pretrial or trial rulings. In addition, Plaintiffs reserve the right to call, either live or by deposition: (a) additional witnesses to provide foundational testimony should any party contest the authenticity or admissibility of any material proffered at trial; (b) substitute witnesses for any identified witness whose employment or other relationship with a company changes such that he or she is no longer able, available, or willing to testify on that company's behalf at trial; (c) any witnesses identified by Amneal or required to rebut Amneal's case; or (d) additional witnesses to respond to issues raised after the submission of this list, such as the testimony of any witnesses who have not yet had his or her deposition taken. Plaintiffs further reserve the right to introduce the deposition testimony of any witnesses who submitted an expert report or declaration on behalf of or in support of Amneal, but who is not called live at trial. Plaintiffs further reserve the right to amend this witness list following completion of the additional discovery ordered by the Court on October 18, 2013 (D.I.200).

EXHIBIT 7

EXHIBIT 7

AMNEAL'S WITNESS LIST

Amneal Pharmaceuticals, LLC ("Amneal") identifies the following witnesses whom it currently intends to call live at trial:

1. **Larry Augsburger,** REDACTED
2. **Richard Bergstrom,** REDACTED
3. **Elaine Gilmore,** REDACTED
4. **Philip Green,** REDACTED

Amneal Pharmaceuticals, LLC ("Amneal") identifies the following witnesses whom it may call (either live or by deposition, as indicated) at trial:

1. **Padmanabh Bhatt** (by deposition)
2. **Woody Bryan** (by deposition)
3. **Richard Chang** (by deposition)
4. **Paul Clark** (by deposition)
5. **Donald Eades** (by deposition)
6. **Brian Johnson** (by deposition)
7. REDACTED
8. **Arash Raoufinia** (by deposition)
9. **Niraj Shah** (by deposition)
10. **Candis Edwards,** REDACTED
11. REDACTED
12. **Stephen Maebius** (by deposition), REDACTED

Amneal reserves the right to call any additional witnesses necessitated by any of the Court's pretrial or trial rulings. In addition, Amneal reserves the right to call, either live or by deposition: (a)

additional witnesses to provide foundational testimony should any party contest the authenticity or admissibility of any material proffered at trial; (b) substitute witnesses for any identified witness whose employment or other relationship with a company changes such that he or she is no longer able, available, or willing to testify on that company's behalf at trial; (c) any witnesses identified by Plaintiffs or required to rebut Plaintiffs' case; or (d) additional witnesses to respond to issues raised after the submission of this list, such as the testimony of any witnesses who has not yet had his or deposition taken. Amneal further reserve the right to introduce the deposition testimony of any witnesses who submitted an expert report or declaration on behalf of or in support of Plaintiffs, but who is not called live at trial. Amneal further reserves the right to amend this witness list following completion of the additional discovery ordered by the Court on October 18, 2013 (D.I. 200).